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CHEMOTHERAPY OF RENAL TUBERCULOSIS

A SURVEY OF TEN YEARS CLINICAL RESEARCH WITH THE DEVELOPMENT OF AN EFFECTIVE ANTIMICROBIAL TREATMENT

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The last ten years have seen a radical improvement of the prognosis of renal tuberculosis. The discovery of streptomycin in the middle of the forties was in itself an epoch-making event, but the first clinical experiments soon showed that if this agent should become of real therapeutic importance, a considerable clinical research would have to be done first. In the middle of the fifties the results of this work, which was performed in many centres all over the world, began to show certain clear lines. Through continued studies and analyses of new series of treated patients we now consider that we are able to state a non-operative form of treatment on the basis of long-term observations which will lead to recovery in about 90 per cent of the cases.

Owing to the smallness of our country an essential part of the treatment of renal tuberculosis and practically all research in connection with this disease have been concentrated in a few places. The present study attempts to give a brief survey of the clinical research which has been performed in the Finsen Institute since 1949 when the first streptomycin was placed at our disposal. The study comprises two epochs: (a) The years up to the end of 1954 when the first series treated with chemotherapeutics had such an extent and such a sufficiently long period of observation that the first large analysis could be undertaken (2, 3, 4), and (b) the period from 1954 through 1958, at the end of which we again analysed the results of the continued observation and possible additional treatment of the initial series, and further analysed a new series treated on the lines crystallized from the analysis of 1954.

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TREATMENT BEFORE THE DEVELOPMENT OF CHEMOTHERAPY

After the introduction of nephrectomy at the end of the last century, unilateral renal tuberculosis soon became a well-established indication for this operation. It was further attempted to improve the results by operating as early as possible, Albarran's "nephrectomie precoce", which to some extent must be considered indicative of an imperfect understanding of the pathogenesis and course of the disease. About 25 per cent of all patients could be cured by nephrectomy; this figure was due to the fact that about half the cases were unilateral, *i.e.* operable, and about half the patients operated on recovered. This percentage of recovery apparently remained almost unchanged until the introduction of chemotherapy. The bilateral cases and those with tuberculosis in the remaining kidney after previous nephrectomy were outside the scope of radical treatment, and were referred to carbon-arc light and sanatorium treatment in various forms. It was difficult to give exact analyses of these forms of unspecific therapy, and hardly any are available. Thus a certain percentage of recovery obtained by these forms of conservative treatment must be added to the percentage mentioned above obtained by operation. The total recovery during this era thus becomes an unknown quantity, which according to the following may possibly have been about 40 to 45 per cent.

At the Finsen Institute, where besides our own failures after nephrectomy we also had many such patients who had been referred from other hospitals to light- and sanatorium treatment, there was ample opportunity to follow the results of this conservative treatment, which was also our only possibility in many bilateral cases. The fact that the removal of a not completely destroyed kidney sacrifices renal tissue capable of function caused us to be more and more conservative in the course of the forties, especially as it appeared

that the possible cause of death in renal tuberculosis was uraemia, *i.e.* the lack of functioning renal tissue, more often than the tuberculosis *per se*. Our conservative attitude was further confirmed by the fact that the course is generally very torpid, and that the disease very often gives no subjective symptoms. The latter became obvious in particular after we introduced in 1943 routine urine inoculation from all patients with extra-urogenital tuberculosis. Consequently, we gradually abstained from nephrectomy in a number of mild cases which would have been operated on according to the earlier policy. Non-destructive cases were treated in the same manner.

In order to have a control series to compare with our first chemo-series, we have analysed the results of this purely conservative treatment in the years 1943—49. The series comprises 90 patients with tubercle bacilluria. These patients have been previously described in detail (3, 4). Here the following survey may be given (Table 1):

Table 1.
The control series.

Total no. of patients	90
Females/males	26/64
Previously nephrectomized	23
Radiological changes in the kidney	21
Ureter tubercle bacilluria	20*)
Previous + present genital tuberculosis	48
Stable conversion	18 (20 per cent).

*) Ureteral catheterization performed in only 37 patients.

Even though the series was limited, certain conclusions could be drawn:

(1) There was a certain natural tendency to recovery.

(2) The course was characterized by pronounced torpidity.

(3) Radiologically the course among the destructive cases was characterized by slow progression of the destructions and the development of new destructions. An exception was formed by the cases which were converted, as the picture was characterized here by exclusion of the affected areas, from a single calyx to the whole kidney.

With the experiences we thus had gained both with regard to the surgical and the conservative treatment it was therefore natural for us when the antituberculosis chemotherapy was introduced to attempt to use this first and foremost as an adjuvant in the continued conservative treatment.

THE ADVENT OF CHEMOTHERAPY AND OUR PRIMARY RESULTS

With regard to the pharmacology of the antituberculous chemotherapeutics and a detailed review of the numerous previous publications on results of experiments with the practical use of the agents, reference may be made to a previous study (4). It may just be mentioned here that the treatment with streptomycin alone was met with a certain optimism, which was kept alive by the first often somewhat rash reports which especially were wanting in period of observation and definition of the effect. As has been the case after the introduction of numerous antibiotics, the optimism was soon replaced by pessimism owing to the numerous recurrences with streptomycin-resistant tubercle bacilli. It was soon almost unanimously established again that nephrectomy was the treatment of choice in unilateral destructive cases, whereas chemotherapy could be attempted in bilateral and non-destructive cases. The introduction of PAS and thus the possibility of preventing or delaying the resistance in simultaneous treatment with this substance did not alter much in the general pro-operative attitude. The interest in the conservative treatment further decreased after S e m b's fine studies on renal resection in tuberculosis (9). The operation, which in S e m b's hands had no mortality at all, whereas, for instance, C i b e r t (1) had 16 per cent of deaths, came into use in many places, and with its sound selective principle it seemed as if it would be the last word in the discussion of the treatment of renal tuberculosis. However, we still continued the conservative therapy, and the first large analysis was finished in the autumn of 1954. The results have been previously published in detail (2, 3, 4). As the conclusions which we published then seem to be valid, and as the conservative treatment gradually seems to gain some ground, we may bring here a summary of the 1954 analysis also with a view to the comparison with our subsequent results.

Series of 1949—1954.

The series comprised 132 patients, 44 females and 88 males, in all age-groups from childhood to old age, the majority being between 20 and 50 years. The average age was higher than that in the control series.

Forty-two per cent had active extraurogenital tuberculosis.

All had tubercle bacilli in catheter urine verified by at least two inoculations. At the beginning of the treatment 70 patients had radiologically demonstrable renal destructions. Fifty-two, including four females, had active genital tuberculosis. In 19 patients neither renal nor genital foci were demonstrated. For various reasons not all the patients had been examined for ureter tubercle bacilluria, but even in patients with definite renal tuberculosis this examination may be negative in a single sample. Positive ureter urines were found in 43 out of 72 examinations in all. Eighty-three patients in all had definite radiological findings and/or ureter tubercle bacilluria. Thirty-five had been previously nephrectomized,

two five months before the beginning of the treatment, the rest of the patients one to 15 years earlier.

From the now probably most commonly accepted hypothesis for the pathogenesis of urogenital tuberculosis (haemotogenous infection of the kidneys, canalicular infection of the male genitals (5, 6, 7, 8)) we have classified the renal tuberculosis of the patients according to Lattimer's table in classes from 0 to 4 according to increasing severity, though we have had to abandon the demand for ureter urines for the reasons mentioned above. Renal tuberculosis of grade 0 thus means that a patient with tubercle bacilli in bladder urine has no demonstrable destructions in the kidneys, whereas he may or may not have positive ureter urines. The composition of the series according to this classification is then as shown in Table 2.

Table 2.
Severity according to Lattimer, old series.

0	62
1	6
2	33
3	17
4	14

Bilateral destructive cases have been classified according to the kidney that was most severely affected.

Chemotherapy.

In 1949 a few patients were treated with streptomycin alone. The results were poor, partly because there were recurrences, and partly because of rather severe side-effects in the form of dizziness. From 1950 we used as a standard course dihydrostreptomycin (DHS) 1 gm daily for three months; at the same time the patients received para-amino salicylic acid (PAS) 12 gm daily for six months in all. From 1952 the administration of DHS was extended, as the patients were given one gm daily for the first two months and then one gm twice weekly for four months. The normal duration of six months was maintained also after the introduction of iso-nicotinic acid hydrazide (INH), which from 1953 was added to the two-drug treatment with 300 mg daily for six months.

Finally, in special cases, other combinations, for instance with Conteben, have been given.

The side-effects of these drugs are so well known that they need not be mentioned. It should be stated, though, that our experiences with streptomycin are so bad that we now only use the pure dihydro-streptomycin (DHS), which in most cases only causes an insignificant treble deafness.

Results.

We have estimated the results or treatment from various points of view, attaching most importance to the most exact factor, the conversion, *i.e.*, cessation of the excretion of tubercle bacilli in the urine. The concept of stable conversion, which we use as the most essential criterion for success, has been defined as cessation of the excretion of tubercle bacilli, verified by at least two inoculations in the course of at least six months *after the end of the treatment*)*.

Further, we have attempted to describe the course of a number of essential factors in patients with renal tuberculosis, such as, for instance, kidney function and the changes in the radiological picture.

With regard to details, reference may be made to a previous monograph, but a summary of the 1954 analysis is given here.

Conversion.

Stable conversion was obtained in 99, or 75 per cent, of the 132 patients, in 75 after one course of treatment and in 24 after two or more courses. Twenty-one have been temporarily converted, whereas 12 have never been negative after discontinuance of the treatment.

One hundred patients received DHS + PAS as a first course. Stable conversion was obtained in 57 of these. Fourteen patients were given INH + DHS + PAS primarily. Stable conversion was obtained in 11, or 79 per cent. The total number of DHS + PAS courses was 120 with a percentage of stable conversion of 52. Similarly, the total number of INH + DHS + PAS courses was 25, leading to stable conversion in 80 per cent. The difference between the value of the two-drug course and the triple-drug course respectively is statistically significant; this was accentuated by the fact that the patients who were given triple-drug treatment had the more severely affected kidneys.

The period of observation for cases with stable conversion was more than three years in 17, from 1½ to three years in 33, and from ½ to 1½ years in 49. A total of 73 had been observed for more than one year.

It was natural to put the prognosis in relation to a number of factors.

The prognosis was the same in either sex.

The age of the patients seemed to play a certain role, as the results were poor both in small children and in elderly patients. In the case of the latter a greater drug intolerance was found to be of essential importance, as it tended towards insufficient doses.

The duration of the tubercle bacilluria was without importance.

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*) We consider it justifiable to speak of stable conversion already after six months owing to the fact that of all recurrences observed after the first chemo-treatment the 92 per cent occurred within the first six months, whereas only four per cent were seen after more than one year. Under practical conditions negative findings for six months thus give a considerable, but, of course, not absolute guarantee for recovery. See also later.

The occurrence of male genital tuberculosis was without conversion-prognostic importance. Nor was epididymectomy, our usual treatment in cases with abscesses, of any importance.

Among 35 previously nephrectomized cases, conversion was obtained in 29, *i.e.* 83 per cent. This figure does not differ significantly from the rest of the series.

The conversion percentage in patients who received carbon arc light and/or sanatorium treatment in addition to chemotherapy was somewhat lower, about 65 per cent. This, however, was hardly due to a deleterious effect of the treatment but rather to a selection of severely affected patients for this treatment.

No prognostic difference could be demonstrated between human and bovine cases.

Significance of the severity of the disease.

Among 70 destructive cases, stable conversion was obtained in 48, or 69 per cent, as compared to 51, or 82 per cent, of the 62 non-destructive cases. Thus there seems to be a tendency to a worse prognosis in the destructive cases, but the difference is not statistically significant. With regard to the conversion within the different groups of severity according to Lattimer (cf. Table 2), the percentage fell with increasing severity as shown in Table 3.

Table 3.

Lattimer's group.	Stable conversion percentage
0	82
1	(67)*)
2	79
3	71
4	43

*) This group was very small.

However, when the phenomenon of varying severity of renal tuberculosis is considered abstractly, it can be described as far as the cavitary cases are concerned as a tuberculous granulation surface of varying size at the border between sound renal parenchyma and the urine in the pelvis plus communicating cavities. Regardless of the size of this surface its two sides will be exposed throughout, each to its constant concentration of chemotherapeutic, namely the concentrations in blood and urine respectively. It can therefore hardly be the extent of the lesions *per se* which determines the prognosis, but any possible decrease of the kidney function and thus of the urine concentration determined by widespread destructions. The reduced kidney function is presumably the most important factor in the treatment of renal tuberculosis.

As might be expected, a rough classification of the patients according to normal and reduced kidney function (the border value was a blood urea level of 40 mg per cent) gave the results shown in Table 4.

Table 4.

Kidney function	Stable conversion
impaired 17	7 = 41 %
normal 115	80 = 80 %

Reverting now to Tables 2 and 3, it appears to be very natural that the number of cases with decreased kidney function rises with the severity. The correctness of the above abstraction presumably appears from the fact that if the frequency of conversion is examined among patients with normal kidney function, it is found to be practically the same within all groups, namely about 80 per cent, in group four even 83 per cent.

Conversion in relation to other factors.

Inoculation of the urine every second to fourth week during the treatment showed that already the result of this examination gave an important prognostic indication. The general rule was that the urine became negative immediately. If all samples remained negative, 68 out of 70 patients, *i.e.* 97 per cent, obtained stable conversion, whereas a more or less irregular conversion was a bad sign (Table 5).

Table 5.

Conversion type	Number	Stable conversion
÷÷÷÷÷	70	68 (97 %)
+÷÷÷÷	13	9 (69 %)
irregular	49	22 (45 %)

Development of resistance to one or more drugs was seen in 21 patients, only seven of whom obtained stable conversion. The development of resistance was most frequently due to the administration of only one drug, more seldom to treatment with two, whereas it never occurred in the course of a triple-drug therapy. An analysis showed considerable interdependence between the three adverse factors: A lowered kidney function, development of resistance, and unsuitable treatment (too small doses, pauses, etc.). The last factor was thus often determined by drug-intolerance owing to the reduced kidney function.

It may be mentioned in conclusion that there seemed to be a poorer prognosis in patients with active extra-urogenital tuberculosis, possibly owing to a general poorer resistance and possibly owing to endogenous re-infection of the kidneys.

Various findings.

Radiologically the typical course of a cavity was that the outlines became more well-defined, and that the cavity often apparently increased somewhat. Both phenomena were presumed to

be due to shedding of debris and necrosis. *Persistent cavities are thus frequent in cured renal tuberculosis.*

Exclusions occurred, though not so frequently as in the control series.

Dilatations owing to strictures of the ureter were rare if present at all. In a few cases, considerable but spontaneously subsiding hydronephrosis was seen, presumably caused by temporarily obstructing debris.

Calcifications most frequently increased, but might also disappear entirely.

It could not be demonstrated that chemotherapy influenced either a normal or a reduced kidney function.

The sedimentation rate showed a falling tendency, which, however, did not definitely exceed the Similar findings in the control series. This seemed to be in accord with the fact that a possible increased sedimentation rate was often found to be due not to renal tuberculosis (which is often associated with a normal sedimentation rate), but to a possible extra-urogenital tuberculous focus, which generally did not benefit as much from the chemotherapy as the renal tuberculosis did.

Conclusions from primary analysis.

The conclusion of the 1954 analysis was that the results of chemotherapy alone were so encouraging that it was practically never indicated to perform nephrectomy primarily. An exception which, of course, always will exist is the unilateral completely destroyed kidney with pyonephrosis, pain and fever, as the chief purpose of the conservative treatment, to preserve renal tissue capable of function, does not exist here any longer. However, it was found that even a complete putty kidney was no indication for operation if it was asymptomatic.

We still considered it correct that a standard course of treatment should last only six months, as 57 per cent obtained stable conversion from this treatment. In the case of recurrence there was still a possibility of obtaining a lasting result if lack of drug resistance permitted repeated courses of treatment, as far as possible with three drugs at the same time. In patients who received such new courses of treatment the stable conversion percentage at the second and the third course, respectively, was 33 per cent and 19 per cent.

The programme for the next five-year period comprised continued control and if necessary and possible, further treatment of the old series, whilst at the same time it should be attempted to ascertain the correctness of the principles deduced in the treatment of new patients. To obtain quite a clear picture of the value of the treatment supposed by us to be optimal, we have in the present new series only included such patients as fulfil the demand that their first course of treatment for renal tuberculosis was started with a simultaneous triple-drug therapy (INH, DHS, PAS) at a time when their tubercle bacilli were fully sensitive to these three drugs. This involves a certain selection, as we have treated numerous other patients who have been treated previously with other courses, or who have started the present course elsewhere as a two-drug therapy. However, this selection does not influence the severity, as will be shown later on. All patients included here have a period of observation of at least six months after the end of treatment, and at least two urine inoculations have been performed during this period.

SECOND ANALYSIS OF OLD SERIES

The analysis was performed as of January 1, 1959. The status with regard to stable conversion appears from Table 6.

Table 6.
Conversion in 132 patients of old series.

	1954	1959
Stable conversion total ..	99 (75 %)	116 (88 %)
Stable conversion solely by chemotherapy	99 (75 %)	115 (87 %)

Table 7.

½—2 years	14 (12 %)	
2—5 »	34 (29.5 %)	
5—7 »	47 (41 %)	58.5 %
over 7 »	20 (17.5 %)	

The period of observation for the converted patients is seen from Table 7. The time has been reckoned from the end of the treatment to the latest urine sample. This also applies in the case of deaths. In most cases it was possible to procure a urine sample in the course of the last half of 1958. The longest periods of observation are now over nine years. With regard to the justification of the previously established criteria for practical recovery, the stable conversion, we have examined how many of the patients who obtained so-called stable conversion in 1954 have had recurrences later on. There were seven recurrences (7 per cent). Five of these have now again obtained stable conversion after another course of treatment, whereas the last two are under or have just finished treatment. The actual percentage of recurrences in this analysis is thus maximally two per cent.

We have analysed these seven patients with regard to common characteristics: All were males, four of whom had or had had a definite genital tuberculosis. Except for one case they all had unquestionable renal tuberculosis, with calcification in only one case. These findings might possibly suggest that the renewed excretion of tubercle

bacilli originated from the male genitalia, as it is our experience that the excretion of tubercle bacilli from these may be somewhat intermittent. However, whatever the focus is, the points of resemblance with regard to treatment are presumably of the greatest importance: None had received a triple-drug therapy. For various reasons four patients had received brief, irregular and interrupted courses, whereas three had received DHS-PAS courses according to our oldest schedule, *i. e.* DHS for only three months.

The improved conversion percentage.

Of 33 patients who in 1954 had not obtained stable conversion, 19 were found stably converted by 1959. In 14 the conversion was due to a second course of treatment, in one to resection under cover of chemotherapy, whereas four converted spontaneously. (Two of these four patients probably had a genital focus, one an eventually completely excluded focus in a single kidney after previous nephrectomy, whereas a destructive focus had never been demonstrated in the last patient, who had bilateral ureter tubercle bacilluria. All four were males).

On January 1, 1959, 14 patients were classified as not definitely converted. However, four of these have died, whereas three failed to appear in spite of numerous summons. Two could not be treated owing to drug-resistance and intolerance respectively. Five have received another course of treatment, one without effect, whereas four have not yet finished treatment.

The relation of the prognosis to various symptoms as well as the description of the course previously given have proved still to hold good. No repetition will therefore be given here, but Table 8 may once more emphasize the importance of the renal function.

Table 8.

Renal function	No.	Stable conv. 1954	Deaths 1954	Stable conv. 1959	Deaths 1959
impaired	17	7 (41%)	3	10 (59%)	5 (29%)
normal	115	92 (80%)	0	106 (92%)	9 (8%)

The total number of deaths during the ten years thus amounts to 14, or 10.6 per cent. Four of the non-converted patients with impaired kidney function died of uraemia, the rest of non-tuberculous diseases, such as heart disease, cancer, and suicide. Fatal renal tuberculosis thus amounts to three per cent in the present series; in this connection it may be mentioned that the course in these cases has been very slow.

ANALYSIS OF NEW SERIES

Since 1954 it has been possible to treat a total of 90 patients on conservative lines with INH + DHS + PAS from the beginning of the course. The results have been analysed for this occasion to give an impression of the optimal therapeutical possibilities in a virgin series. The patients in whom the course was started with INH, DHS and PAS but who for some reason or other had to continue with another, possibly minor combination, have also been included, so that the results should hold good for practical clinical use. The description of the series with regard to severity etc. appears from Table 9, where the corresponding percentages in the old series are given for comparison.

Table 9.
Composition of the new series.

	Number	Percentage	
		present series	old series
Total material	90		
Females	31	34.4	33
Males	59	65.6	66
Destructive cases	68	76	53
Ureter tubercle bacilluria..	51	57	32.6
Ureter tubercle bacilluria and/or radiol. renal destr.	76	84.5	63
Impaired renal function ..	7	8	13
Previously nephrectomized	9	10	26
Distribution in the various Lattimer groups: 0	22	24	47
1	8	9	4.5
2	28	31.1	25
3	12	13.4	13
4	20	22.2	10.6
Age over 50 years	29	32.2	19.7

The table seems to show distinctly that this new series is composed of essentially more severe cases than the old one. The number of cases with impaired renal function is, however, somewhat smaller, but the difference is far from being significant. On the other hand the number of cases of unquestionable renal tuberculosis appears to be much higher, and the distribution within the various groups of severity shows a tendency to larger destructions. Of the 68 cases with radiological destructions, 17 were bilateral, whereas four had been previously nephrectomized.

As in all similar series there was a considerable number of cases with male genital tuberculosis. Of the 59 males, 48 thus had demonstrable genital tuberculosis at the beginning of the treatment. Of 46 males with unquestionable renal tuberculosis, 38 had genital tuberculosis. Conversely, of 49 males with present or previous genital tuberculosis, 40 had present or previous unquestionable renal tuberculosis. Forty-three cases of tuberculosis of the prostate gland were ascertained, on palpation alone in 10, by radiography in 11, and both radiographically and palpatory in 22. There were 33 positive findings in a total of 57 urethrographed males with tubercle bacilluria, *i. e.* 58 per cent. Sixteen patients were epididymectomized during the course of treatment.

Results.

Table 10 demonstrates that it was impossible to establish any subgroups of the series, so that significant differences with regard to the stable conversion appeared. It may thus be mentioned that 17 cases with bilateral destructions all obtained stable conversion. The most amazing finding here is no doubt that an impaired renal function in contradistinction to the previous series had no deleterious effect. However, the group is small, and with the given border value many of the impairments found with regard to the renal function will be modest. Altogether, however, especially this result must weigh much in favour of the value of the triple-drug therapy.

Table 10.
Results in new series.

	No.	Stable conversion	Per cent
Total material	90	82	91
Females	31	29	93.5
Males	59	53	90
Destructive renal tuberculosis	68	61	90
Previously nephrectomized	9	8	89
Impaired renal function	7	7	100
Male genital tuberculosis at the beginning of the treatment	48	43	90

Four patients had died at the time of the follow-up. All four had obtained stable conversion, and none of the deaths was caused by renal tuberculosis.

The period of observation for the 82 patients who obtained stable conversion is given in Table 11. As before, the time is reckoned from the discontinuance of the treatment. Of course, the periods of observation cannot be very long here. However, the average corresponds to the periods of observation which we reported in 1954; with our experience with regard to the frequency of recurrences there is reason to presume that a subsequent analysis at least will not show much lower figures.

Table 11.
Period of observation for patients with stable conversion in the new series.

Time	No.	Per cent
6—12 months	21	25.6
1—3 years	40	49
3—5 »	20	24.4
over 5 »	1	1.2

Number of courses.

Eighty-four patients have received only one course of treatment, *i. e.* six months' chemotherapy, whereas six patients have had two courses. Of the 84 patients, 78, or 93 per cent, obtained stable conversion; *i. e.* the stable conversion in 95 per cent of all who obtained this, or in 87 per cent of the whole series, was obtained after one course of treatment. In 18 patients, side-effects of different nature necessitated either a pause or a change in the course.

Development of drug-resistance.

As was to be expected, no development of resistance was observed following the simultaneous treatment with INH + DHS + PAS. In the whole series only one case of resistance was observed; this was a case of INH-resistance in a patient who received the combination INH + Conteben + PAS during the second course of treatment.

The radiological course.

This series of patients was not followed radiologically so intensely as the earlier series, partly because we felt that we had already previously ascertained the radiological course, partly because of the irradiation hazard. Therefore it is not possible to describe the course in 15 cases, whereas we found conformity with our previous statements in the rest of the cases. In eight patients the cavities had thus increased, in 32 their size remained unchanged. In two cases there seemed to be a real reduction in size, whereas exclusions of varying extent were seen in 11 cases. It may therefore be stressed again that the general rule is that the cavities persist in patients who have obtained stable conversion.

Only once did we observe an unquestionable development of hydronephrosis and hydroureter, which, however, seemed to be due to a malignant tumour of the bladder.

The non-converted patients.

Eight patients did not obtain stable conversion with chemotherapy. Three of these were of the type severe unilateral renal tuberculosis, where it was thought, however, that chemotherapy ought to be attempted. These three patients were later nephrectomized, as they could not be converted permanently and still had symptoms from the kidney.*) Further five patients with rather slightly affected kidneys also failed to respond permanently to one or two courses. The predominant common feature in these five patients was no doubt psychic deviations with regard to character or intelligence, which gave rise to inappropriate courses, as the patients did not take their drugs regularly, or threw them away etc. The only patient with development of resistance also belonged in this category. There is, of course, a possibility of repeated treatment, but the prognosis is no doubt poor.

*) After 1954, two patients who theoretically fulfilled the conditions for being included in the present series have been primarily nephrectomized without preceding attempts at conservative treatment. The indication was a unilateral, completely destroyed kidney with symptoms.

DISCUSSION

A comparison between the old and the new series seems to show clearly the superiority of a rational triple-drug therapy. True, the final results obtained, namely 87 per cent and 91 per cent of stable conversion in the old and the new series respectively, are practically identical. However, the time in which this result was obtained was 10 and four years, respectively, and furthermore the last series was composed of more severe cases. To obtain a direct numerical comparison, it seems relevant to compare the results of the first course administered in the two series. In order further to clarify the picture we shall here only consider the first DHS + PAS course, which was the prototype in the old series. As previously mentioned, the stable conversion percentage was here 57 (57/100). The first course in the new series gave a stable conversion of 87 per cent (78/90). The difference is highly significant.

The mortality can hardly be estimated comparatively, as most of the patients died of non-tuberculous diseases. This also applies to the four patients in the new series who died.

The fact that the final conversion percentage in the two series is almost the same might suggest that we have here reached an if not biological then practical limit for what can be obtained. The figure also corresponds to what S e m b (9) obtained in his selected series of resections. Therefore, the prognosis for the remaining 10 per cent should presumably be considered from a somewhat pessimistic point of view, especially if it is so that the patients' mental deficiency plays an essential part here.

With regard to the development of resistance, the new series has fully confirmed our suppositions from the 1954 analysis that a triple-drug therapy consistently carried through minimizes the risk of the development of resistance in renal tuberculosis. A fact that gives rise to some anxiety is therefore that some phthisiologists still use two-drug courses, for instance, INH + PAS, as a standard therapy.

CONCLUSION

As the result of ten years' work with chemotherapy as the most essential treatment of renal tuberculosis we feel justified in venturing the statement that the time of experimental treatment can now be considered finished in all essentials. Renal tuberculosis responds so extremely well to a rational chemotherapy that it is indicated in all cases with intact tissue to preserve in a tuberculous kidney to treat conservatively with INH + DHS + PAS for six months. Experience shows that there is no reason to treat the patients longer than six months to begin with, as such a course will produce stable conversion in about 85 to 90 per cent of the patients. The combination mentioned will practically obviate the risk of development of resistance so that the treatment may be repeated if necessary.

A putty kidney which gives no symptoms is not in itself an indication for operation. But in cases with a very severely or completely destroyed kidney which gives rise to fever, pain, haematuria, etc., the conservative chemotherapy has no purpose, as there is nothing to preserve. Here nephrectomy under cover of chemotherapy must be recommended.

Resection of the kidney will seldom be indicated but may be considered where a chemo-resistant recurrence may be attributed with certainty to a definite localized focus. In this connection it may, however, be strongly emphasized that persistent cavities after a chemo-course suggest nothing about activity, as the radiologically characteristic picture of a chemotherapeutically healed renal tuberculosis just is persistent, well-defined cavities. Ignorance of this phenomenon has, according to the literature, led to many superfluous and thus harmful kidney resections.

It may be pointed out in conclusion that the results reported here are due to intense work in a specialized department whose physicians have taken a special interest in renal tuberculosis and whose nurses and assistants have been trained especially in nursing and controlling these patients. It should be realized that the good results obtained do not mean that urogenital tuberculosis is now a less serious disease which can just be treated with some tablets. Physicians or departments intending to undertake the treatment of renal tuberculosis must consider beforehand whether they have at their disposal the necessary knowledge and patience and laboratory facilities for the control over years which is required. A badly started course of treatment may often aggravate the prognosis considerably, which is unforgivable the more so as renal tuberculosis practically never requires acute treatment.

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TECHNIQUES AND COMPLICATIONS IN THERAPEUTIC ABORTION

By HELGE G. BERTHELSEN and ERLING ØSTERGAARD

During the past years, various methods have been employed as a means of inducing therapeutic abortion. The following may be mentioned among those generally employed in Denmark: Dilatation with laminaria rod and subsequent evacuation of the uterus, vaginal hysterotomy, puncture of the ovum, dilatation by Hegar's method + evacuation, injection of cremor saponis, and abdominal hysterotomy. All these methods in turn have been employed in the Gynaecological Department of Frederiksberg Hospital.

Our own and others' experience led us in due course to abandon the use of the laminaria rod, vaginal hysterotomy, and puncture of the ovum, and until further restrict ourselves to three methods, used along the following lines: 1) Dilatation according to Hegar's method + evacuation in one seance in pregnancies up to and including the tenth week, 2) injection of cremor saponis in pregnancies older than ten weeks, 3) abdominal hysterotomy + sterilization, when the last-mentioned intervention has also been indicated and the pregnancy has been beyond the tenth week. In pregnancies earlier than the tenth week, where indications for sterilization are present in addition, therapeutic abortion is first carried out by dilatation according to Hegar's method + evacuation followed by laparotomy and sterilization by Madlener's method three days later.

The aim of this report is to give a detailed account of both the technique employed in these three interventions, and the primary complications which have arisen from the interventions, assessed on the basis of our material from the years 1953—57.

MATERIAL

Table 1.

Distribution of therapeutic abortions performed by year and method.

	Dil. Heg. + evac.	Cremor saponis	Abd. hysterotomy + ster.	Total
1953	102	241	22	365
1954	58	161	21	240
1955	84	180	22	286
1956	55	128	18	201
1957	52	72	19	143
Total	351	782	102	1235

Table 1 gives a survey of the material; it is seen that the number of abortions has been falling in the period in question, the figure for 1957 being less than half that for 1953. A total of 1,235 interventions have been performed during this period of five years, and the percentage distribution of the methods mentioned has been as follows: Just under 30 per cent for dilatation by Hegar's method + evacuation; somewhat over 60 per cent for injection of cremor saponis; and under 10 per cent for abdominal hysterotomy + sterilization. An account will be given below of the technique and the complications arising from the various methods.

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DILATATION AND EVACUATION

As mentioned in the introduction, we employ this method for interrupting pregnancies up to and including the tenth week, as in these relatively early pregnancies it is unnecessary to dilate to more than at the most Hegar No. 26 (diameter 13 mm), which can usually be done gently and without risk of damage to the cervix.

Technique:

The intervention is carried out under general anaesthesia, usually pentothal + N_2O-O_2. Local anaesthesia has been used at the same time, five ml one per cent lidocain with adrenaline injected into the loose connective tissue on each side of the cervix on a level with the internal uterine orifice. By this means the dilatation of the cervix is facilitated and the muscular tone of the corpus uteri is increased (Hansen 1948). After the usual disinfection of the vagina, gentle dilatation is performed, not more than the age of the pregnancy demands, *e. g.*, in the eight week to Hegar No. 16—18 (diameter 8—9 mm), in the tenth week to Hegar No. 26 (diameter 13 mm); the dilatation is facilitated by dipping the Hegar pins in sterile oil. The evacuation is performed with a not too sharp currette; if the uterus becomes too atonic during the intervention, one ml of Methergin® is administered intravenously. Intrauterine lavage or packing is never performed.

Complications:

Table 2 is a survey of the observed primary complications by use of this method, the material having been arranged into groups according to the age of the pregnancy. A total of 54 complications arose in 351 cases, corresponding to about 15 per cent. If first-day fever is not included, there have been 36 cases with complications, corresponding to about 10 per cent of the total number.

Haemorrhage, which occurred in 16 cases, has been counted as a complication when the condition required intervention, *e. g.*, blood trans-

Table 2.

Survey of number of interventions and complications in dilatation and evacuation, in groups according to age of pregnancy.

Age of pregnancy in weeks Number of interventions (total 351)	6-9 173	10-12 172	13-1 6	> 16 0	Total
Temp. ≥ 38° C. first day	8	9	1	0	18
" " several days	1	6	0	0	7
Haemorrhage	3	12	1	0	16
Adnexitis	3	5	0	0	8
Perforation + laparotomy	1	2	0	0	3
Rupture of cervix	0	1	0	0	1
Collapse	1	0	0	0	1
Total	17	35	2	0	54

fusion, re-evacuation or injection of uterotonic drugs over and above any given at the actual evacuation.

In eight cases, the follow-up showed tenderness and infiltration of the adnexa, presumably indicating inflammatory changes. A temperature rise (≥ 38° C.) lasting more than one day was observed in seven cases, perforation of the corpus uteri followed by laparotomy in three cases and rupture of the cervix in one case. One patient collapsed following injection of local anaesthetic, but rallied quickly.

If the distribution according to the age of the pregnancies is examined, it appears that in the two equally large groups of interventions carried out in the 6—9th and 10—12th week, apart from first-day fever there are about three times as many complications in the 10—12th week group as in the 6—9th week group, namely nine and 26 complications respectively.

In the few cases where dilatation and evacuation was carried out after the 12th week of pregnancy, the patients were those in whom the cremor saponis has either been ineffective or has caused such pronounced bleeding that spontaneous discharge of the foetus could not be waited for. Finally, in a couple of cases it was necessary to carry out the intervention in one seance on account of the patient's mental condition, in spite of the advanced age of the pregnancy.

CREMOR SAPONIS

Barns in 1947 reported the experience from University College Hospital, London, with respect to "71 cases of therapeutic abortion by means of soft-soap pastes", and on the basis of this experience, our department took up this method for therapeutic abortion in 1952. The principle of the method is to produce total or partial loosening of the ovum by means of an intrauterine, extraovular deposition of cremor saponis, so that the ovum is discharged by a mechanism similar to that in spontaneous abortion.

As mentioned previously, the method is used for therapeutic abortion after the tenth week of pregnancy, as after that stage of the pregnancy the ovum can be reckoned to close the uterine opening of the Fallopian tubes, so that the injected cream remains in the uterus. That this is the case is shown by a study from the department in 1956 (Schou et al.), in which the injection of cremor saponis to which radiopaque medium was added showed no flow into the Fallopian tubes or the peritoneal cavity in 43 cases controlled by roentgenogram, whereas in two cases in the tenth week there was flow into the Fallopian tubes.

Technique:

The intervention is performed without anaesthesia. The patient lies in position for a vaginal operation, and the usual disinfection of the vagina is carried out.

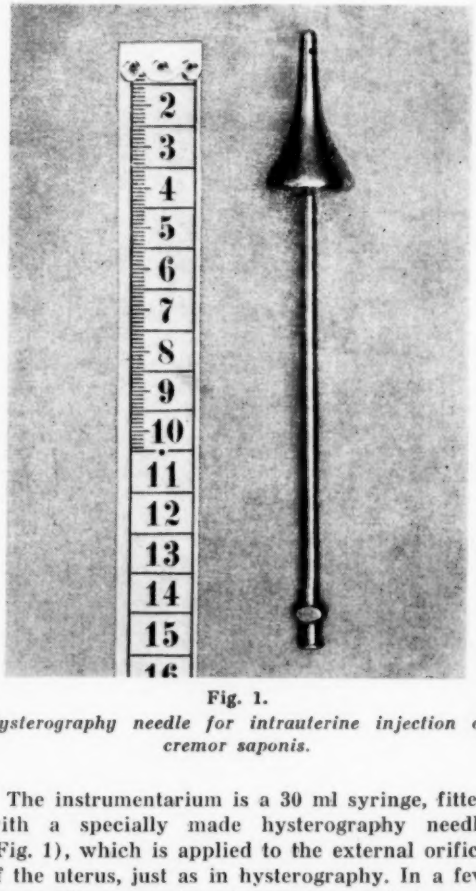

Fig. 1.

Hysterography needle for intrauterine injection of cremor saponis.

The instrumentarium is a 30 ml syringe, fitted with a specially made hysterography needle (Fig. 1), which is applied to the external orifice of the uterus, just as in hysterography. In a few cases, where sequelae of previous cervical lacerations made it impossible for the needle to fit sufficiently tightly, it was necessary to perform the injection through a soft rubber catheter, advanced a couple of cm past the internal orifice of the uterus.

The cream used is prepared and sterilized at the hospital dispensary, as a modification of the cream used at the University College Hospital.

Cremor saponis sterilisat. F. H.:

I	Cetylanum	g	60
	Acidum oleinicum	g	80
	Acidum stearinicum	g	320
	Oleum arachidis	g	800
II	Chlorcresolum	g	2
	Aqua rec. dest.	g	2230
III	Sol. natrii hydrox. 20 vol %	g	164
	Sol. kalii hydrox. 20 vol %	g	344
		g	4000

The substances mentioned in section I are melted on a water bath. A warm solution of II, produced by dissolving cresol chloride in the warm water, is added to I, shaking all the time. Finally, the mixture is emulsified by adding III. The soap cream so produced is filled while still warm into 100 ml vials in amounts of 50 g, and then sterilized for one hour at 120° C. The preparation is described as a cream, as insufficient base is added to saponify all the fatty substance. On preparation, the pH is about 8.0, but on standing the pH of the soap rises to a little above 9.0.

The amount of cream employed is roughly proportional to the age of the pregnancy. As a rule, about 15 ml is injected + one ml for each week of pregnancy. The actual injection of the cream takes place without any noteworthy discomfort to the patient, if a carefully observed and very slow rate of injection is observed, *i. e.*, 4—5 ml per minute.

After the injection the patient remains in bed for about two hours. She then receives 30 g castor oil and thereafter remains up until the foetus is discharged. As soon as the foetus is discharged an intramuscular injection of one ml Methergin ® is given, whereby the haemorrhage is reduced, so that the currettage carried out in all cases after the discharge of the foetus can usually be delayed until the next morning.

Should the foetus not be discharged in the course of the next 24 hours, the patient receives on the following day, while up, tabl. ergopakini*): one tablet per hour, six times in all. If necessary, this procedure is repeated on the following day. If the abortion has not taken place or is not under way in the course of the third day, the cremor injection is repeated on the fourth day. Only in a few cases has the cream been injected three times. As a rule, the patients are discharged from hospital on the third or fourth day after currettage.

In a previous report (S c h o u et al., 1956) an account has been given of the effectiveness of the method. Of 650 cases, 91 per cent discharged the foetus after one injection and a further three per cent after two or possibly three injections. In just under four per cent of the cases, the abortion started but had to be terminated by instrumental evacuation before the foetus was discharged, mainly on account of too profuse haemorrhage. In just over two per cent the method was ineffective and for these cases other treatment had to be used.

*) Ergopakin FH contains: Ergometrin 0.02 mg, quinine hydrochloride 25 mg, and papaverine hydrochloride 10 mg per tablet.

Complications:

Table 3 gives a survey of the observed primary complications with the method, the material having again been grouped according to age of pregnancy.

Table 3.

Survey of incidence of complication in the cremor saponis method in groups according to age of pregnancy.

Age of pregnancy in weeks Number of interventions (total 782)	6-9 7	10-12 407	13-16 294	> 16 74	Total
Temp. ≥ 38° C. first day	1	45	29	10	85
" " several days	0	11	7	3	21
Haemorrhage	2	8	14	3	27
Adnexitis	1	6	6	2	15
Rupture of cervix	0	0	0	1	1
Collapse	0	1	0	0	1
Total	4	71	56	19	150

There have been a total of 150 complications in 782 cases, corresponding to about 19 per cent; if first-day fever is not included, there have been 65 complications corresponding to eight per cent. Haemorrhage, regarded as a complication along the same lines as in dilatation and evacuation, was observed in 27 cases.

Infection of the adnexa was demonstrated in 15 cases, rupture of the cervix in one case and collapse in one case. The last-mentioned case occurred in a 44-year-old patient pregnant for the fourth time, where the indications for therapeutic abortion were previous complicated deliveries (preeclampsia, retention of the placenta in the last two deliveries, with considerable haemorrhage). Further, the patient suffered from bronchial asthma, considerable varicose veins, and had also shown signs of a chronic stress neurosis during some years. The patient was in the 10—11th week, and 18 ml cremor was injected without difficulty. About two minutes after the injection the patient became unwell, moaning, with weak pulse, slight sweating, but fully conscious. 0.5 mg adrenaline was injected i. m., and the patient rallied rapidly. The cremor injection did not bring about abortion, and therapeutic abortion was carried out three days later by dilatation and evacuation.

The grouping according to the stage of pregnancy shows that also in this method, excluding first-day fever, there is a slightly higher incidence of complications in advanced pregnancies, rising with increasing age of pregnancy.

The seven cases figuring in the column 6—9th week originate from the first experimental period with the method, where cremor was also used

before the tenth week in a few cases for experimental reasons.

ABDOMINAL HYSTEROTOMY AND STERILIZATION

This intervention is carried out when sterilization is to be performed at the same time as the abortion procedure, in the case of pregnancies older than the tenth week; before this stage, the abortion procedure and the sterilization are carried out in two seances.

Technique:

General anaesthesia. Laparotomy, minor classic Caesarean section, digital evacuation of uterine cavity, which is thereafter curretted with a blunt abortion curette; immediately following evacuation of the uterus, Pitupartin ® one ml is injected, followed by Methergin ® one ml intravenously.

The uterine incision is sutured in three layers with catgut, the most superficial one as an atraumatic peritoneal suture.

The sterilization is carried out according to Madlener's method, a loop of the Fallopian tube on both sides is pinched off and ligated with silk, after stitching through the mesosalpinx.

Complications:

Table 4 shows that there were a total of 74 complications in 102 interventions. If first-day fever is excluded, there were 49 complications, corresponding to a complication incidence of 50 per cent; if fever of several days' duration is also excluded, 12 complications were recorded in the 102 cases. Five of these were cases of haemorrhage, three of them were cases of post-operative pneumonia, and two were cases of inadequate wound healing. Ileus and phlebitis were each recorded once.

Table 4.

Survey of the number of interventions and complications in abdominal hysterotomy and sterilization, in groups according to age of pregnancy.

Age of pregnancy in weeks Number of interventions (total 102)	6-9 4	10-12 31	13-16 47	> 16 20	Total
Temp. ≧ 38° C. first day	0	7	13	5	25
" " " several days	3	12	16	6	37
Haemorrhage	0	1	3	1	5
Ileus	0	1	0	0	1
Pneumonia	0	1	2	0	3
Phlebitis	0	0	1	0	1
Inadequate wound healing	0	0	1	1	2
Total	3	22	36	13	74

The greater complication incidence with more advanced pregnancies, as observed in the methods previously mentioned, has not been found in this method, where the incidence of complications (less first-day fever) is practically the same in the three groups, 10—12th, 13—16th and more than 16 weeks.

Our intervention in four cases prior to the tenth week of pregnancy has been contrary to our general principles.

LETHALITY

No death has occurred in the present material of 1,235 cases.

DISCUSSION

The reasons for abandoning the methods previously employed in this department: Laminaria rod, vaginal hysterotomy, puncture of the ovum, are the complications associated with these methods. Quite frequently, the use of laminaria rods turned out to be followed by inflammatory complications. Kühnel found the same result in his material from 1951.

For a period, therefore, we employed vaginal hysterotomy in cases where the uterus was too large for treatment with dilatation by Hegar's method + evacuation in one seance. However, after we ourselves found two cases of endometriosis in the wound and in the fundus of the bladder following the use of this method, and became aware of the remarkable incidence of this complication in Swedish series (Brosset 1954, Gottlieb 1957, Arén 1958), we have also abandoned this method, which in addition involves a rather demanding technique.

The method of puncture of the ovum which was recommended in 1948 by Oram has been tried in 50 cases, but on account of a relatively high incidence of complications and a prolonged course (Schou 1951), we gave up this method in favour of the cremor method which also in Oram's material (1956) was shown to have a lower incidence of complications than puncture of the ovum.

In recent years, therefore, we have exclusively employed the three methods evaluated in the present study, according to the lines mentioned above.

The analysis of the results has shown that no death has occurred after the use of these three methods in a total of 1,235 cases of therapeutic abortion.

With respect to complications, these occurred with an incidence of about ten per cent when using dilatation and evacuation (first-day fever excluded), more or less in line with the analysis by Trolle (1950) and Kolstad (1957). This shows that the method has an incidence of complications of about ten per cent even under the most favourable conditions in a gynaecological department. Our material shows in addition that the incidence of complications is three times as great in the group 10—12th week as in the group 6—9th week. This method should therefore be the method of choice in early therapeutic abortion, in which the incidence of complications is lowest (five per cent).

The incidence of complications in the cremor saponis method was found to be eight per cent (first-day fever excluded). Considering that this method is used by preference in the more advanced pregnancies, and as Trolle (1950) and Svanberg (1948) among others have shown a rising incidence of complications with increasing age of pregnancy, the eight per cent must be considered as remarkably low. In the present material, if the complications are compared which have arisen in therapeutic abortion in the 10—12th week, using dilatation and evacuation and cremor saponis, respectively (Tables 2 and 3), it appears that there have been 26 complications with the former in 172 cases (first-day fever excluded), and 26 complications with the latter in 407 cases, a significantly lower incidence. After the tenth week, therefore, the cremor method must thus be considered as more gentle than the more mutilating interventions, and produces a therapeutic abortion whose course much resembles that of the spontaneous one. The method is, however, not altogether without risk, as fatal cases have been reported in this country (Berthelsen & Østergaard 1958 and Brandstrup 1958).

The cremor employed is hardly ideal, but presumably can be improved and made completely safe even with possible accidental injection into vessels.

The laparotomies show a relatively high incidence of complications, even when fevers are excluded. The more serious complications also occur here, such as may possibly have a fatal course. This also appeared clearly in our material from the whole country (1958), in which most of the deaths occurred following abdominal hysterotomy and sterilization (lethality: 1.3 per thousand).

CONCLUSIONS

Using the technique described in the present study, therapeutic abortion by dilatation and evacuation has an incidence of complications of about ten per cent, varying from five per cent before the tenth week of pregnancy to 15 per cent after the tenth week of pregnancy; the incidence is eight per cent with injection of cremor saponis, and 12 per cent with abdominal hysterotomy and sterilization (50 per cent when fever is included).

The incidence of complications increases with increasing age of pregnancy.

The cremor saponis method is more gentle than dilatation and evacuation (after the tenth week of pregnancy). The age of the pregnancy should therefore be included in the considerations of choice of method and evaluation of the risk involved in the intervention.

A certain reserve is advisable in the use of the method of abdominal hysterotomy and sterilization because of the greater risk involved in this intervention.

SUMMARY

The present report describes the technique and complications in 1,235 cases of therapeutic abortion carried out in the Gynaecological Department at Frederiksberg Hospital during the years 1953—1957. The following methods were used:

Dilatation by Hegar's method + evacuation in pregnancies younger than the tenth week, injection of cremor saponis in pregnancies older than the tenth week, and finally, abdominal hysterotomy and sterilization when indications for sterilization were present after the tenth week.

The study has shown that therapeutic abortion by dilatation + evacuation has a complication incidence of about ten per cent, varying from five per cent before, till 15 per cent after the tenth week of pregnancy; that the frequency is about eight per cent by the cremor saponis injection method, and about 12 per cent (50 per cent when fever is included) by abdominal hysterotomy and sterilization.

The frequency of complications increases with increasing age of pregnancy. There have been no deaths in connection with the interventions performed.

It is concluded that cremor saponis is a more gentle method than dilatation + evacuation, in pregnancies older than the tenth week. The age of the pregnancy should be included in the considerations of the choice of the method. A certain reserve is advisable in the use of abdominal hysterotomy and sterilization.

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LETHALITY AND INCIDENCE OF COMPLICATIONS IN THERAPEUTIC ABORTION IN DENMARK, 1953—1957

By HELGE G. BERTHELSEN and ERLING ØSTERGAARD

This investigation is based on notifications to the National Health Service of therapeutic abortions performed in Denmark during the years 1953—1957.

MATERIAL

As indicated in Table 1, the material is divided into 6 groups according to the method employed. The group "Other vaginal methods" consists of puncture of the ovum, intrauterine catheter, and intrauterine injection of formaldehyde. As the table shows, 23,666 notifications of therapeutic abortion were made in the course of five years. After a peak of 5,434 notifications in 1955, the number declined in the course of the subsequent two years to 3,775 in 1957. It will be observed that in spite of the fall in the total annual interventions as mentioned, the use of cremor saponis has been increasing steadily throughout the five years in question, so that in 1957 this was method most frequently employed, with a total of 1,415 notified cases. Throughout the entire period, this method has been used in 3,869 cases. In addition, there has been a steady increase in the number of abdominal hysterotomies + sterilization. The remaining methods have correspondingly decreased in incidence throughout the same period.

Complications:

Table 2 gives a survey of the number of complications and deaths in the various methods used for therapeutic abortion. It appears from the table that in 3,869 cases in which cremor saponis was employed, there have been 80 complications and two deaths. The corresponding figures for dilatation and evacuation are 322 and three, for a total of 9,429 cases. With the laminaria rod and subsequent evacuation in 2,554 cases, the figures are 78 and four. Among 204 notifications of vaginal hysterotomy there are reports of three complications, with no deaths. In the group "Other

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Table 1.

Survey of the distribution of the material according to year and method used. The group designated "Other vaginal methods" consists of puncture of the ovum, intrauterine catheter and intrauterine injection of formaldehyde.

	1953	1954	1955	1956	1957	Total
Cremor saponis	253	392	753	1,056	1,415	3,869
Dil. Heg. + evacuatino	2,326	2,459	2,337	1,496	811	9,429
Lam. rod. + evacuation	589	647	697	451	170	2,554
Other vaginal methods	712	612	567	273	126	2,290
Vaginal hysterotomy	81	62	42	14	5	204
Abdominal hysterotomy	834	968	1,038	1,232	1,248	5,320
Total	4,795	5,140	5,434	4,522	3,775	23,666

Table 2.

Survey of the incidence of complications and deaths in the various methods of therapeutic abortion.

	Number	Complications	per 1000	Deaths	per 1000
Cremor saponis	3,869	80	21	2	0,5
Dil. Heg. + evacuation	9,429	322	34	3	0,3
Lam. rod + evacuation	2,554	78	31	4	1,6
Other vaginal methods	2,290	101	44	0	0
Vaginal hysterotomy	204	3	15	0	0
Abdominal hysterotomy	5,320	113	21	7	1,3
Total	23,666	697	29	16	0,7

vaginal methods", consisting of 2,290 patients, the figures are respectively 101 and 0. Finally, in 5,320 cases of abdominal hysterotomy + sterilization, 113 complications and seven deaths were reported.

In all, out of 23,666 cases of therapeutic abortion, 697 complications were reported, corresponding to 29 per thousand, and 16 deaths, corresponding to 0.7 per thousand.

The incidence of the complications is seen from Tables 3 and 4. It is likely that only the more

Table 3.

Survey of notified non-fatal complications grouped according to incidence in the various vaginal methods.

	Crem. sap.	Dil. Heg. + evac.	Lam. rod + evac.	Other vag. metods	Vaginal hyster-otomy	Total
Fever	17	66	43	44	0	170
Haemorrhage	27	88	19	21	0	155
Adnexitis	30	65	6	17	1	119
Perf. of uterus	0	72	4	6	0	82
Rupture of cervix	1	18	1	8	0	28
Phlebitis	1	6	2	3	1	13
Pulm. infarct.	0	4	1	0	0	5
Collapse	2	0	1	0	0	3
Peritonitis	1	0	0	1	0	2
Pneumonia	0	2	0	0	0	2
Pyometra	1	0	0	1	0	2
Bladder lesion	0	0	0	0	1	1
Oliguria	0	0	1	0	0	1
Septicaemia	0	1	0	0	0	1
Total	80	322	78	101	3	584

Table 4.

Survey of non-fatal complications in abdominal hysterotomy (5,320 cases).

Rupture of wound etc.	24
Haemorrhage	20
Pulm. infarct.	19
Fever	12
Post-operative ileus	10
Phlebitis	8
Pneumonia	8
Intraperitoneal haemorrhage	4
Parametritis	4
Bladder lesion	2
Pulm. atelectasis	1
Intestinal lesion	1
Total	113

severe complications have been reported, thus constituting this material. The complications associated with abdominal hysterotomy have been placed in a special group on account of the special nature of this intervention.

It is remarkable that there have been 82 perforations, almost all occurring in the group dilatation and subsequent evacuation, and corresponding to an incidence of eight per thousand for this group. In addition, there have been 18 cases of rupture of the cervix in this group. The haemorrhages are more or less uniformly distributed with about the same percentage incidence for the different methods. Another remarkable feature is that fever occurs more infrequently with cremor than with the other vaginal methods. According to the notifications, the two cases of collapse in the cremor group developed following the cremor injection; both patients rallied. In the laminaria group there is one case of collapse which cannot be further elucidated. There was one case of lesion of the bladder following vaginal hysterotomy.

Thetotal incidence of complications for the vaginal interventions is 584 out of 18,346 cases notified. corresponding to 32 per thousand.

Table 4 deals with abdominal hysterotomy and shows that the complication with the greatest reported incidence was incomplete wound healing in 24 cases, this designation comprising rupture of the wound, haematoma or wound abscess. There were 19 cases of pulmonary infarction and ten cases of post-operative ileus, three of these necessitating re-laparotomy. There were two bladder lesions and one intestinal lesion.

Lethality:

The majority of deaths occurred after abdominal hysterotomy, seven deaths being notified from this; five of these deaths were caused by embolism of the pulmonary artery. One patient died in uraemia following rupture of the wound and peritonitis. One patient died in shock and hyperpyrexia.

Four of these deaths occurred following the use of the laminaria rod with subsequent evacuation. Two of these patients died of septicaemia. One patient died from unsuspected haemorrhagic diathesis two days after the intervention. One patient died of air embolism in the heart and brain.

Three deaths occurred after dilatation and evacuation: In one case death occurred immediately following laparotomy for rupture of the uterus, in one case death occurred from paralytic ileus and peritonitis after perforation of the uterus, and in one case from embolism of the pulmonary artery 17 days after the intervention.

In two cases death occurred immediately following injection of cremor saponis probably as a result of cremor injection into the vessels.*)

DISCUSSION

As expected, the result of the investigation shows that therapeutic abortion carries a certain, although slight, lethality. In our material from the last five years, this has been 0.7 per thousand as a mean of all the methods employed.

*) After finishing this work a case of death following the cremor saponis method has been reported (Brandstrup 1958).

Oram (1952) assesses the mean lethality in therapeutic abortion in Denmark from 1940—50 at two per thousand, of which he calculated 1.2 per thousand as being a result of the actual intervention. Klintskog (1953) gives an account of the lethality in therapeutic abortion in a collected material from Sweden. The material amounts to about 35,000 cases for the period 1935—51, the mean death rate being assessed at 1.58 per thousand, but the death rate has been falling throughout the period mentioned, thus being 1.1 per thousand from 1949—51, as a mean of all methods. The lethality with abdominal hysterotomy with sterilization was 5.1 per thousand for the whole period, falling to 2.7 per thousand for the period 1949—51. It is probable that the lethality has fallen further since, but the figures from Sweden suggest, just as ours do, that the abdominal interventions carry a greater lethality than the vaginal ones.

Of the different methods which have been used for therapeutic abortion in our material, abdominal hysterotomy and sterilization carries the greatest lethality (1.3 per thousand) and the most serious complications (wound rupture, infarction and ileus), but on the other hand, the incidence of complications has been lower than in the vaginal methods.

The lethality in the vaginal interventions is low — about 0.5 per thousand — approximately the same as is associated with pregnancy and birth. There were a small number of deaths with each of the three most frequently used methods, cremor saponis, dilatation by Hegar's method + evacuation and laminaria rod.

The risk in dilatation by Hegar's method is above all perforation of the uterus and rupture of the cervix; in our material these complications have occurred in 90 cases, in two of these with fatal outcome. In the laminaria rod method the risk is primarily infection, and two of the deaths were due to septicaemia.

There were no deaths following the use of the "Other vaginal methods", but of these, the method of puncture of the ovum carries a relatively high incidence of complications.

No death occurred in 204 cases of vaginal hysterotomy, but in a not insignificant number of cases this method was followed by endometriosis in the hysterotomy scar and in the base of the bladder. Partly on account of this by no means rare and relatively serious complication, and partly on account of the technique in this intervention being somewhat more difficult, the use of this method has been declining and it was only employed five times in the entire country in 1957.

In the vaginal methods, the mean incidence of complications has been 32 per thousand. Comparing the incidence of complications in the most frequently used methods in our material (Table 2), it appears that cremor saponis has the lowest and the group "other vaginal" the highest incidence. Considering that the cremor saponis method is preferably used with relatively advanced pregnancies, the low incidence of complications in this method may be regarded as remarkable. Furthermore, the complications which have developed have been of a less serious character than in the other vaginal interventions. In particular, there have been no cases whatever of perforation of the uterus, and only in one case was there rupture of the cervix. The two cases of transient collapse must be considered as serious complications, and are presumably due to cremor injection into the vessels.

CONCLUSION

All methods of therapeutic abortion involve a certain slight lethal risk or risk of supervening complications.

The vaginal methods in current use have a lethality risk of about 0.5 per thousand and the abdominal interventions a corresponding risk of about 1.3 per thousand. The incidence of complications in the various vaginal methods varied between 20 per thousand and 45 per thousand, significantly lowest for cremor saponis, which must be considered as being the most gentle of the present methods used for therapeutic abortion, *but not even this method is without lethal risk.*

References:

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Press discussion not desirable.

THERAPEUTIC ABORTION ON ACCOUNT OF X-RAY EXAMINATION DURING PREGNANCY

By ERLING HAMMER-JACOBSEN

In recent years X-ray examination of pregnant women has in some instances been either the sole or a contributory indication for therapeutic abortion.

Eleven pregnant women had one or more abdominal X-ray examinations during the first three months of pregnancy. Therapeutic abortion was later performed in eight cases while three went to term.

EARLIER STUDIES

It is not intended to make here a complete list of studies previously published. This was recently, and most thoroughly, done by Magnusson (1955 and 1958), by Gyllensteen (1958) and earlier by Murphy (1947).

Previous studies of injury to the foetus due to irradiation almost exclusively originate from the use of radiation doses of a quality and quantity corresponding to those of radiation therapy. For this reason it is difficult to apply conclusions drawn from these doses to the comparatively small doses in diagnostic radiology, and more animal experiments will be required using diagnostic units and with foetal doses ranging from about one r to 10—20 r.

As the *background radiation* is about 0.1 r per annum a foetus after the normal term of pregnancy will have received a presumably harmless dose of about 0.08 r, which should be considered in relation to the doses mentioned later.

Animal Experiments.

By exposing pregnant mice to radiation, Russell & Russell (1950) produced malformations of the thoraco-lumbar skeleton. The smallest dose applied was 25 r, and this produced changes. Russell & Russell (1952 and 1956) and Russell (1954) proved that the earlier in pregnancy the radiation was given, the more malformations would result from such radiation, and that the period from the second till the sixth week of human pregnancy is particularly sensitive. As the effect of radiation varies continuously with the dose, apparently without any threshold, the authors are of the opinion that smaller doses will also cause injury to human beings, in whom even small defects are recognized. However, doses less than one r are assumed not to cause visible injury.

Wilson (1954) found retardation of growth at the rate of one to five per cent when exposing pregnant rats to radiation with 12.5 r, the smallest dose hitherto used in animal experiments. With a dose of 25 r retardation of growth and malformations of the eyes were produced at the rate of six to twelve per cent and six per cent respectively.

Hicks (1954) showed that neuroblasts of foetuses of rats and mice necrotized after a dose of 40 r.

Tahmisian & Wright (1958) found that the incidence of malformations in grasshoppers increased from 50—80 per cent when the dose rate was increased from one r/minute to 200 r/minute. The total dose in both instances was 250 r. For the purpose of radiography with modern units and short exposures the dose rate may be, for example, 50—150 r/minute.

The *United Nations'* report (1958) mentions that *in vitro* it has been possible to produce changes in embryonal neuroblasts by application of a dose of one rad. The nature of the changes was not described.

Diagnostic Radiology.

Murphy (1929) and Goldstein & Murphy (1929 a) discuss a woman who had been subjected to two retrograde pyelographies, with several exposures, at her 5th—6th week of pregnancy. At the end of term she gave birth to a mongoloid idiot who died a few days after delivery. On a rough estimate the foetal dose is assumed to have been 5—25 r.

Kjellberg (1942) mentions an instance of hysterosalpingography in pregnancy. In spite of the application of 120 ccs. contrast agent the patient did not miscarry. There is no mention of the child.

Valdemar Madsen (1942), in his material, mentions a 25-year-old married woman who was subjected to a hysterosalpingography in 1938, eight days after her latest menstruation. The pregnancy had a normal course and the patient gave birth to a healthy normal term infant.

From the Department of Radiology
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Rigshospitalet, University of Copenhagen, and
the Radium Centre, Copenhagen
(Head: Professor *Jens Nielsen*).

Børge Nielsen (1946) mentions two cases of hysterosalpingography in pregnancy. One completed her normal term, the other continued until the eighth month when pregnancy was interrupted during eclampsia. In 1947 the same author mentions that hysterosalpingography was performed in four pregnant patients. One of these aborted, but hardly due to the X-ray examination. The children are not mentioned, but a follow-up study together with an estimation of the dose might be interesting.

Hultberg (1949) mentions a 25-year-old unmarried woman who twice had her abdomen exposed to radiation from a photofluorographic apparatus in the third month of her pregnancy in order to induce abortion. These exposures were given by a roentgen technician (the father of the child) and each exposure lasted about five minutes during which the woman stood pressing her abdomen against the roentgen tube. In the fourth month of pregnancy an X-ray burn of the abdomen occurred. The patient gave birth to a 15 days premature infant weighing two kilos. The child, who was followed up to the age of 13 (Hultberg 1959), has an unusually small head. He is unable to read, and can only express himself by sentences of not more than five words each. It has been recommended that he should be admitted to a home for imbeciles. There is no particular somatic disease. The foetal dose has not been recorded but is assumed to be of the order of 50—100 r.

Kaiser & Marvin (1957) counted the white blood corpuscles in 22 newborn children whose mothers had been subjected to abdominal X-ray examination in the 8th—9th month of pregnancy with a foetal dose of 1.5—3 r. No difference was found in the number of blood corpuscles in children exposed to X-rays and in the unexposed ones.

Stewart, Webb & Hewitt (1958) carried out a large and careful investigation of the causes of leukaemia and cancer in infancy. The mothers of 1,416 children who died in the years 1953—1955, under the age of ten, of leukaemia (677 cases) or cancer (739 cases) were interviewed. The control material was of an identical size. The total number of children who had died was 1,694 but only 1,416 cases were covered by the study.

A significantly higher frequency of direct foetal irradiation, virus infections, and threatened abortions, was found amongst the dead children, and a high maternal age also seemed to increase the risk of leukaemia in infancy. Among the dead children there was also a higher post-natal frequency of X-ray examinations, acute pulmonary infections, and severe injuries.

In the leukaemia-cancer group 178 (15 per cent) of the mothers — as against 93 (seven per cent) of the mothers of the control group — had been subjected to abdominal X-ray examination during pregnancy. Eighteen of the 178 X-ray examinations were performed during the first half of pregnancy. In the control group the corresponding figure was only two out of 93. Even if the material from the first half of pregnancy is small, the figures seem to emphasize the greater risk involved by irradiation in early pregnancy.

Considering that 86 per cent of the sick infants died without having been exposed to pre-natal X-ray irradiation, and that 7 per cent of the healthy infants had been exposed to irradiation without subsequent diseases, the irradiation can only be the cause of some of the cases. It might be concluded that abdominal X-ray examination is responsible for 14 per cent less 7 per cent = 7 per cent of leukaemia-cancer cases.

However, one may also make the following calculation: Out of 565 deaths per annum 40 (7 per cent) should be caused by abdominal X-ray examination (mainly pelvimetry and abdomen obstetric) in pregnancy. In England about 12 million X-ray examinations are carried out per annum at the hospitals (Osborne & Smith 1956). 0.5—1 per cent of these are pelvimetry or obstetric examination of the abdomen = 60,000 to 120,000 per annum. In Sweden the corresponding figure is 0.4 per cent (Larsson 1958).

Thus one may estimate that only about $^1/_3$—$^2/_3$ per thousand of these examinations are causing leukaemia or cancer in the child. This figure should be compared with the number of lives saved by the information obtained by these X-ray examinations. The foetal doses have presumably been of the order of two to ten r.

In 1958 Dempster followed-up the children of 148 mothers in whom pelvimetry had been performed in 1948. Out of 125 children traced 104 were alive and healthy. Among the 21 who died there were no cases of leukaemia or cancer.

Radiotherapy.

Following radiotherapy several instances of foetuses injured by radiation — and also a few normal children — have been reported but the foetal doses have been of the order of some hundred r and not at all comparable with diagnostic radiology.

Robinson (1927), Goldstein & Murphy (1929 a and b), and Murphy (1929), report several cases in which mothers had had abdominal X-ray or radium treatment and then gave birth to children with various malformations (microcephaly, hydrocephaly, spina bifida, strabismus, malformation of cranium and extremities).

Jones and Neill (1944) report on 56 patients who during pregnancy received radium or X-ray treatment of cancer of the uterine cervix. Among the children were found seven definitely abnormal and 12 definitely normal ones.

Lacomme (1931) and Hobbs (1950) report on three normal children after radiotherapy of the abdomen of the mother in the 2nd—3rd, 4th, and 5th month of pregnancy respectively.

Injury to the foetus has been reported also after atomic bomb explosions (Yamazaki, Wright & Wright 1954), and after experiments with animals with *radioactive isotopes* (Sikov, Lofstrom & Noonan 1958). The doses have been of the order of 500—1,000 r and are not comparable with the doses of diagnostic radiology.

Summing up one can say that we know very little about possible injuries to foetuses on account of the small radiation doses in diagnostic radiology. The therapeutic abortions mentioned later on were thus performed on a very slight basis.

MATERIAL

The present study comprises 11 pregnant women who were subjected to one or more abdominal X-ray examinations during the first three months of pregnancy (cf. Table 1).

The X-ray examinations were performed in five radiological departments in Copenhagen in the years 1954—1958. The inductions of abortion were performed in two gynaecological departments and two surgical departments in Copenhagen. Five of the abortions were induced in the same gynaecological department.

The histories of the 11 patients and the three children have been studied. For reasons of discretion the three children were not followed-up but in a few years it is intended to try to get further information about the children.

Calculation of foetal dose.

With a view to calculation of foetal dose the patients' X-ray films have been studied. The technical data were received from the radiological departments in question: focus-film-distance, thickness of the added aluminium filtration of the tube, the tube voltage applied (kV), tube current (mA), time of exposure (sec) and the total number of mAs.

Rectal or vaginal dose measurements in patients of various radiological departments have been used for the calculations. Some of the measurements have previously been reported (Hammer-Jacobsen 1957 a, b).

The vaginal dose is assumed to be equal to the dose in the uterus, that is, the foetal dose. In order to calculate the dose in the uterus in relation to the rectal dose, measurements have been made in a paraffin phantom (Hammer-Jacobsen 1957 a), and later with Mix D phantom blocks, at the Radiophysical Laboratory of the Radium Centre. It is found that the dose at a depth of 10 cm ("uterus") is two or three times as large as at a depth of 15 cm ("rectum"), when using radiation of diagnostic quality.

For the purpose of the calculations the foetal dose has been assumed to be twice that of the rectum (antero-posterior projection).

In patients Nos. I, III, IV and VII dose measurements were made with the actual X-ray units that had been used when these patients were examined.

There is a very wide scatter of both the measured and the calculated doses. The mean value is the most probable dose but one cannot be certain that the patient in question has not received the maximum possible dose. The maximum possible dose must be decisive when considering the indication for induced abortion. The wide scatter may be due to, among other factors, variable duration of fluoroscopy.

CASE HISTORIES

The cases are presented in the order of the decreasing size of the calculated foetal dose.

I. 24 years old, married, first pregnancy. Always regular menstruation. In 1954 the patient underwent X-ray examination of abdomen, intestinal passage, 2 barium enemas, and intravenous pyelography, 48—63 days after last regular menstruation. Foetal dose is calculated to be 3.7 r (1.1—18.9). The examination took place during an admission to a surgical department.

After discharge the patient was referred to the Institute of Human Genetics by her physician, with a view to ascertaining whether the X-ray examinations performed might be harmful to the foetus. As a radiologist was of the opinion that the X-ray examinations could not be considered an indication for induced abortion the patient was allowed to continue to term.

Natural birth at expected date, 2050 g, 45 cm. One half of the placenta was said to be fibrously transformed. Premature looking child with the following diseases during the first 3½ years after birth: 3 weeks old: strangulated hernia ing. dxt. 3 months old: strangulated hernia ing. sin. Following this two pneumonia-type illnesses. From the age of two years asthma (asthma in the family). EEG at the age of two years: normal. At the age of two years acute appendicitis. The child could not sit until it was eight months old, walk until it was 18 months, or speak until it was two years old. Not until it was 3½ years old did it develop and look like other children of its age. Data available up to the age of four years.

II. 26 years old, married, two normal deliveries 1953 and 1955. An abortion 1954 in the 3rd month of pregnancy. During an admission to a medical department in 1956 the patient underwent X-ray examination of chest, barium enema, barium meal, intestinal passage and cholecystography 21—37 days after her last menstruation. During a previous pregnancy her menstruation had been fairly regular during the first months. Bufo test positive. Foetal dose calculated to be 1.7 r (0.5—6).

The radiological department estimated a foetal dose of 5—10 r, and as the Institute of Human Genetics stated that the possibility that the irradiation had injured the foetus could not be excluded, an abortion was induced about one

month later. A foetus was not observed, but microscopy of the scrapings showed: "small pieces of necrobiotic decidua and villi chorii covered with a single layer epithelium and with natural vasofaction. In addition particles of foetal cartilage and foetal bone as well as other elements from the foetus are seen: no malignancy."

III. 39 years old, unmarried, first pregnancy. Always regular menstruation. During admission to a surgical

Table 1.
X-ray examination during pregnancy.

Case No. (Year) X-ray examinations	Total mAs Foetal dose	No. of days after last menstrual period	Induced abortion or delivery	Foetus at abortion or child at birth
I. (1954) Abdomen Intest. passage Barium enema Barium enema I. v. pyelography	? > 9,000 mAs *3.7 r* (1.1—18.9)	48—63	Delivery (normal)	2,050 g, 45 cm. 9 months' pregnancy. No malformations. Half the placenta had undergone fibrous degeneration.
II. (1956) Chest Barium enema Barium meal Intest. passage Cholecystography	? > 5,000 mAs *1.7 r* (0.5—6.0)	21—37	Induced abortion	Micr. exam.: Normal placental tissue. Foetal cartilage and bone without malignancy.
III. (1958) Barium enema Cholecystography Barium meal	Approx. 2,500 mAs *1.5 r* (0.4—3.0)	42—49	Induced abortion	Grossly normal. No bony deformities on X-ray examination.
IV. (1956) Lumbar spine Thoracic spine	Approx. 1,800 mAs *0.6 r* (0.07—1.6)	58	Delivery (normal)	3,800 g, 53 cm. 9 months' pregnancy. Lumbar myelocele.
V. (1957) Lumbar spine	Approx. 840 mAs *0.4 r* (0.05—1.2)	15—16	Induced abortion	Not examined
VI. (1958) Lumbar spine Thoracic spine Pelvis	Approx. 1,020 mAs *0.4 r* (0.07—1.1)	14—18 (35)	Induced abortion	Micr. exam. of curettings showed normal placental tissue. Foetus not observed.
VII. (1958) I. v. pyelography	Approx. 1,200 mAs *0.4 r* (0.2—0.5)	88	Induced abortion	Grossly normal. Micr. exam. of cerebral tissue, placenta and umbilical cord normal.
VIII. (1958) Lumbar spine	Approx. 200 mAs *0.09 r* (0.01—0.2)	27—21	Delivery (normal)	2,750 g, 50 cm. 9 months' pregnancy. Normal child.
IX. (1956) Hysterosalpingography	Approx. 300 mAs *0.06 r* (0.02—0.2)	36 (7)	Induced abortion	Grossly normal. Micr. report has disappeared.
X. (1957) Hysterosalpingography	Approx. 250 mAs *0.05 r* (0.01—0.1)	21 (7—14	Induced abortion	Not examined.
XI. (1957) Hysterosalpingography	Approx. 150 mAs *0.03 r* (0.01—0.08)	35 (11)	Induced abortion	Not examined.

department the patient underwent barium enema, cholecystography, and barium meal, 42—49 days after latest regular menstruation, and 16—23 days after a very shortlasting and slight menstruation two days before scheduled time.

The patient has given the exact dates of coitus which took place only once every month. On this account one is in the rare position of being able to establish with reasonable probability, that the barium enema was made on the 25th day after conception, cholecystography on the 31st and barium meal examination on the 32nd day.

The patient petitioned the Danish Mothers' Aid Centre (D. M. A. C.) in Copenhagen for a therapeutic abortion, as she had read in "Readers Digest" that an X-ray examination may cause an abnormal development of the foetus. Further she stated that as she was 39 years old, she was afraid of having a mongoloid child, that she lived alone without any possibility of being married to the father of the child, and that her financial position was difficult. Phantom- and patient-dose measurements were made with the same X-ray unit, letting the physician in charge of the fluoroscopy of the patient make a fluoroscopy of another patient, and a foetal dose of 1.5 r (0.4—3) was calculated. The barium enema accounted for 95 per cent of this.

On the basis of these findings the D. M. A. C. decided to permit the induction of abortion, attaching about three fourths of weight to the radiation risk and about one fourth of weight to the other circumstances. Abortion was induced in the 16th week. The foetus was 17 cm long without any malformations. Radiographs of the foetus show no skeletal malformations. Sectioning showed nothing macroscopically abnormal.

IV. 26 years old, married, one normal delivery six years earlier. During treatment at a physiotherapy clinic for lumbago X-ray examination of the lumbar spine and thoracic spine was performed 58 days after her latest regular menstruation. Foetal dose: 0.6 r (0.07—1.6).

A double lumbo-sacralization was found in the mother. During the pregnancy the risk of injury due to irradiation was not considered and induced abortion was not discussed. Yet the patient is admitted to this material because of diagnostic irradiation of abdomen in early pregnancy.

Normal delivery at term, 3800 g, 53 cm. Congenital 4 × 5 cm myelocele of the lumbar region. The myelocele epithelized spontaneously after one year, but the motor development has been slow and it is probable that sphincter vesicae does not function normally. Cranial circumference a couple of centimetres larger than normal. X-ray examination of cranium (age: 14 days) shows a peculiar coarse netting, probably due to lack of calcification. The spine seems to be normal, but laminae are not seen clearly in the region of the third lumbar vertebra. The child has been in hospital and treated as an outpatient at a neurosurgical department. As it has been considered desirable not to contact the patient, information about the child after its first birthday is not available.

V. 34 years old, married, one normal pregnancy three years earlier. Always regular menstruation. During treatment at a physiotherapy clinic the lumbar spine was X-rayed 15—16 days after latest regular menstruation. Foetal dose: 0.4 r (0.05—1.2). 98 days after the latest menstruation the following statement was entered in the journal of the physiotherapy clinic, "The patient turns out to be in the third month of pregnancy".

The patient was then admitted to a gynaecological department and because of the risk due to irradiation, abortion was induced 138 days after latest menstruation. Unfortunately the foetus, measuring 30 cm, was not examined.

VI. 22 years old, unmarried. At the age of 20 an abortion in the third month. At the age of 21 one normal delivery. Always irregular menstruation: 8 days/2—6 weeks. During admission to a gynaecological department the thoracic spine, the lumbar spine and pelvis were X-rayed because of an earlier diagnosed onsetting ankylosing spondylitis. The X-ray examinations were made about five weeks after her latest menstruation of normal duration, and 14—18 days after a short-lasting (3 days) menstruation. Foetal dose: 0.4 r (0.07—1.1).

As a gynaecological examination 8 days later showed uterus of pregnancy consistency and as the Bufo reaction was positive, evacuatio uteri was performed 11 days after the X-ray examinations, because of the risk of injury due to irradiation. Foetus was not observed. Microscopy of the scrapings: "Numerous villi chorii, a few of these containing small vessels. Also slight remnants of corpus endometrium with a few glands in the proliferation stage, and a single flake of decidua tissue, are observed. No signs of specific inflammation or malignancy".

VII. 22 years old, married, two normal deliveries four years ago and 10 months earlier. Regular menstruation. In the third month of pregnancy, 88 days after the latest regular menstruation the patient was referred, at a scientific follow-up, for intravenous pyelography. After two exposures the X-ray nurse became aware that the patient was pregnant and the examination was discontinued. Foetal dose: 0.4 r (0.2—0.5).

Three weeks later the patient petitioned the D. M. A. C. in Copenhagen for a therapeutic abortion on account of a chronic bladder inflammation and of varicose veins, because it was too soon after her last child's birth, and on account of lack of living accomodation. She had tried to induce abortion by means of pills. On request the radiological department in question gave the information that "injury to the foetus in the above patient can not be left out of consideration for certain, but the risk is considered to be slight". At the recommendation of the D. M. A. C.

abortion was induced on a medical and eugenic indication in the 18th week of pregnancy.

Foetus measured 33 cm and was autopsied at the Pathological-Anatomical Institute of the University of Copenhagen. The macroscopic examination showed natural conditions. On microscopy of the umbilical cord, both cerebral hemispheres and the occipital lobe, the brain stem, and medulla spinalis, nothing abnormal was observed. Microscopy of the placenta showed "flakes of decidua tissue and homogeneous eosinophilic stained matter, calcified here and there", otherwise nothing pathological. P. D.: "Foetal brain tissue without pathological changes. Placenta tissue without definite pathological changes, yet showing calcifications. Thus no signs of radiation-injury".

VIII. 25 years old, married, previously two abortions. During treatment at a physiotherapy clinic the lumbar spine was X-rayed 27—21 days after latest menstruation. Foetal dose: 0.09 r (0.01—0.2).

In view of the radiation hazard a gynaecologist stated that he considered induced abortion absolutely indicated. Another gynaecologist and two radiologists on the other hand stated that there was no indication for induced abortion. It was then decided to let the patient complete the pregnancy. The patient has not been informed about the considerations.

Normal delivery eight months and 26 days after the first day of the latest menstruation. Child without malformations: 2750 g, 50 cm. Normal development. Data available up to the age of five months.

The following patients are three married women who were exposed to hysterosalpingography at a gynaecology department with subsequent therapeutic abortion at the decision of the gynaecology department. One might at first think that the department had considered the possible risk involved by the contrast injection in uterus as well as the possible radiation hazard; but it is stated that the contrast injection was not taken into consideration.

IX. 24 years old, first pregnancy. Menstruation during the last year somewhat irregular, 4—5 days/4—7 weeks. On account of dysmenorrhoea a hysterosalpingography was performed 36 days after the latest menstruation of regular intensity, seven days after a slight bleeding. Foetal dose: 0.06 r (0.02—0.2). (Six films without fluoroscopy). Radiological description (Fig. 1): "A round smooth cavity of the size of a grape-fruit, in which the right uterine corner may be discerned, is filled, but the greater part of the interior of this cavity is filled by a globular, slightly humpy clearing going from the left side and located at anterior or posterior wall. Radiological diagnosis: Pregnancy". Bufo test positive.

In view of the radiation hazard abortion was induced 11 days after the X-ray examination. A 15 cm long foetus was delivered, showing nothing abnormal macroscopically. It is stated that tissue was sent for histological examination but the report of the microscopic examination has been mislaid.

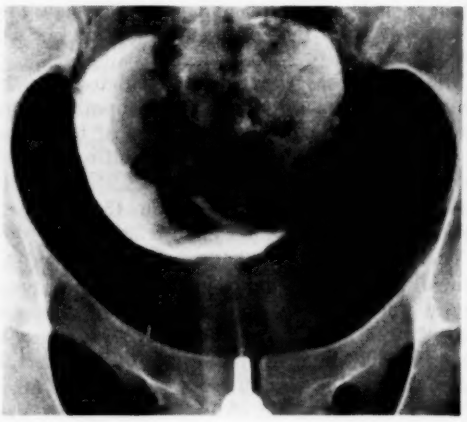

Fig. 1.
Case no. IX. Hysterosalpingography. Pregnancy.

X. 34 years old, one natural birth 10 years ago. Referred to a gynaecological department for metrorrhagia. Menstruations previously regular, but of variable intensity, and at varying intervals the last three months. Hysterosalpingography was performed about three weeks after latest menstruation of a moderate and short-lasting character, 1—2 weeks after a very faint and short-lasting bleeding. Foetal dose: 0.05 r (0.01—0.1). The uterine cavity was about 10 cm × 10 cm and there was an oval clearing at the centre and to the right, almost the size of a hen's egg. Radiological diagnosis: "It must be a pregnancy at about the 3rd month". Subsequently evacuatio uteri was performed "as the patient by now has got a rather high X-ray dose". Some abortion tissue which was not microscopically examined was removed.

XI. 32 years old, two normal deliveries 13 and 6 years earlier. Referred to a gynaecological department for observation for cancer of the uterus. Irregular menstruation for two to three months. Hysterosalpingography was performed 35 days after latest menstruation of natural intensity, 11 days after a sparse and short-lasting (1½ days) menstruation. Foetal dose is calculated to be 0.03 r (0.01—0.08). The uterine cavity was considerably enlarged with a large round defect in the right half. Radiological diagnosis: "Fibroma uteri? Pregnancy?". Bufo test positive. "In addition it turns out that the patient has had rubella. On account of this and on account of the X-ray examination it is thought there must be an indication for induced abortion". Evacuatio uteri was then performed and foetus and placenta were removed, but not examined.

It is characteristic of these three patients that they all had had irregular menstruation and all were in the second to third month of pregnancy. They were all gynaecologically examined prior to

the X-ray examination without their pregnancy being detected. Further it is paradoxical that the pregnancy was diagnosed by X-ray examination and that the pregnancy was then interrupted on account of the X-ray examination.

Finally, as a curiosity, a case encountered once by the D. M. A. C. will be discussed. A woman applied for induced abortion because her husband had been exposed to several X-ray examinations in regions near to the gonads. The patient is not included in the relevant material as the problem is of a genetic nature and does not directly concern foetal injuries.

43 years old, married, three children 18, 15 and 11 years old, applied to the D. M. A. C. for induced abortion as she thought she was too old to have a child, and that she was not strong enough. There are three cases of diabetes and one case of insanity in the patient's family. After careful investigation the application was refused.

The application was renewed and this time she claimed that her husband had been exposed to 20—30 intravenous pyelographies during recent years. A gonad dose of 15—40 r was estimated and the Institute of Human Genetics stated on this basis that there was an eugenic indication for therapeutic abortion. A closer investigation revealed, however, that only 12 intravenous pyelographies and one barium meal examination, together with two abdominal survey pictures were undergone. On this basis the application was once more rejected by the "Nævnet angående Svangerskabsafbrydelse" (Council on Therapeutic Abortion), stating that "one has insufficient basis for assuming that X-ray doses like those of the present case may involve obvious risk of serious foetal injury".

Normal delivery at term. Fully developed child: 3900 g, 52 cm. Normal physical and mental development. Information available up till age of 13 months.

DISCUSSION

The aim of the casuistic material produced is to draw attention to this new indication for therapeutic abortion. On the other hand it is not intended to try to either prove or disprove that the diseases in the children of patients I and IV are due to X-ray irradiation at the foetal stage.

It is desirable to invite reports on similar cases and to arrange at the Institute of Human Genetics a central registration of patients who are exposed to irradiation during the first half of pregnancy.

Three questions may be raised for discussion:

1) What foetal doses are injurious?
2) Has therapeutic abortion been justified in the cases submitted?
3) How can irradiation of pregnant women be avoided?

1. *Injurious foetal dose.*

Russell & Russell (1956) are of the opinion, as previously mentioned, that doses below one r may be presumed to produce no measurable adverse effects.

The *International Commission on Radiological Protection* 1957 recommends that pregnant women are not occupationally exposed to irradiation but that no special precautionary measures need to be taken if the maximum permissible weekly dose is not exceeded. For the first four months of pregnancy this corresponds to a foetal dose of about one r. (Skin dose: 300 mr/week).

On this basis one might suggest the following general lines for the first four months of pregnancy:

Foetal doses of less than about one r, according to our present knowledge, are presumed to cause no noticeable injury, and consequently provide no indication for therapeutic abortion.

Foetal doses between about one r and about 10 r are assumed, in some instances, to cause injuries in the form of diseases, malformations, slow development or reduced resistance, especially when the irradiation occurs between the second and sixth week. Doses should be individually evaluated after measurements with the X-ray units in question. If there are additional indications, therapeutic abortion should be assumed advisable.

Foetal doses above about 10 r are assumed to involve a rather great probability of foetal injury. In such cases induction of abortion should therefore be the general rule.

These limits are thought of as a suggestion for discussion. The limits are not sharply defined ones, they should be open for individualization. More animal experiments with doses ranging from one r to 10—20 r will perhaps afford a basis for determination as to whether there is a threshold dose and establish the dependency between dose and incidence of disease or malformation. Studies of larger clinical materials may likewise lead to more definite rules.

During the last five months of pregnancy it seems as if the foetus will withstand rather considerable doses, of the order occurring in pelvimetry.

If abortion is performed, the foetus should always be microscopically examined. When birth follows irradiation of a foetus with doses exceeding about one r the development of the child should be kept under observation.

2. *Has induced abortion been justified in the cases submitted?*

These abortions, induced on account of the radiation hazard, were performed according to the "eugenic" indication of the Pregnancy Act: "Where there is an obvious risk that the child, on account of hereditary taint, or for reasons of injury or disease contracted at the foetal stage,

will be suffering from insanity, imbecility, other severe mental defects, epilepsy, or serious and incurable abnormality or bodily disease".

It appears from the material that there has been considerable uncertainty as to the evaluation of the risk and the indication for abortion.

In accordance with the above mentioned preliminary lines one might think that patient No. I should have had her pregnancy interrupted. Patient No. IV should also perhaps have had her pregnancy interrupted, if there were additional indications. On the other hand it must be agreed that patient No. VIII should be allowed to continue her pregnancy.

Regarding the abortions induced it seems that the indication was reasonable in patient Nr. III, and perhaps also in case No. II. The same applies to patient No. VII, where the medical indication seems to have been predominant, and patient No. VI who was unmarried and had one child.

On the other hand there seems to be no reason to induce abortion in patients Nos. V, IX, X and XI. In patient No. XI it should be mentioned, however, that the patient stated she had had rubella during pregnancy. However, a specified time or any verification of rubella is not mentioned.

All cases should perhaps have been submitted to the D. M. A. C. for decision.

3. *How can irradiation of pregnant women be avoided?*

Through the years several authors have warned against irradiation in early pregnancy. Already in 1935 Østergaard Christensen stated: "Considering the very great and disastrous sensitivity to radiation of the young foetus, it cannot beforehand be left out of question that even diagnostic doses may be dangerous when applied to the female pelvic region during early pregnancy".

In 1958 Brøndsted stated: "In the future it will require an enormous effort of vigilant control to protect, not only pregnant women, but also potential mothers, against the radiation hazards".

As about 4,000 legal abortions are induced in Denmark per year (Berthelsen & Østergaard 1958) the patients mentioned here do not represent any quantitatively great problem. But as the problem is fundamental and its treatment may create a precedent it has been found reasonable to deal with it.

The most important conclusion must therefore be the necessity for the establishment of a simple measure of precaution that will prevent irradiation of foetuses in early stages.

As most women in the early part of the period especially sensitive to radiation (second to sixth week) may not yet have realised their pregnancy, Russell & Russell (1952) suggest that irradiation of pelvis in women at the reproductive age should be restricted to the two weeks immediately following menstruation, as during that time the chance of an undiscovered pregnancy is but small. After the sixth week there need not be any doubt of pregnancy and irradiation should therefore be avoided according to general practice. This suggestion was mentioned in an editorial of Ugeskr. Læger 1956, by Brøndsted (1956), Hammer-Jacobsen (1957a), Buhl (1957), Martin (1957) and Dupont (1958).

In order also to avoid irradiation in women with ovulation early in the cycle, and with a special view to the irregularly menstruating patients mentioned in this material, the following modification of the suggestion is proposed: —

In fertile women X-ray examination of the abdomen should be performed only during the first ten days following a regular menstruation of normal intensity and duration.

This rule should be introduced as a routine rule by all radiological departments, practising radiologists and chiropractors. The physician referring the patient for X-ray examination should state the latest date of menstruation in the reference, and the nurse should check that no more than ten days have passed.

If the possibility of pregnancy cannot be excluded, X-ray examination should be avoided or postponed until the last five months of pregnancy. Only vitally indicated examinations should be exempted from this rule.

It might be thought that observation of this rule would cause too much disturbance in the daily routine. Against this it must be pointed out that it affects only about 3 per cent of all X-ray examinations (male + female). Approx. ½ mill. X-ray examinations of women are carried out per year in hospitals and by practising radiologists (Hammer-Jacobsen 1958). Through investigations to be published later it can be calculated that about 30,000 abdominal X-ray examinations of women 15—39 years old (excl. pelvimetry and abdomen obstetric) are carried out. About 300 of these women are in their first month of pregnancy.

Approximately every fifteenth reference of a woman to X-ray examination will involve consideration of the latest menstruation in relation to the X-ray examination.

Many radiological departments are already observing this rule where hysterosalpingography is concerned. Considering this, no inconvenience should be necessary in trying to have the rule observed. Even in the largest radiological department in Denmark the number of these patients will hardly exceed ten a day (outpatients + inpatients). The problem will in particular concern outpatients.

CONCLUSION

Very little is known about the possible injurious effect of small radiation doses on foetuses in early pregnancy. It will be necessary to carry out more

animal experiments with foetal doses ranging from one r to 10—20 r and to follow-up children exposed to irradiation in the first half of pregnancy.

Irradiation of the foetus should as far as possible be avoided during the first half of pregnancy, as long as we do not know more about these matters.

It is suggested that the following rule should be introduced as a routine: —

In fertile women abdominal X-ray examination should only be performed during the first ten days following a regular menstruation of normal intensity and duration.

If this rule is observed the problem of therapeutic abortion on account of X-ray examination during pregnancy may be avoided in the majority of cases.

SUMMARY

Previous studies on radiation injury to the foetus are reviewed. Very little is known about possible injuries due to the small radiation doses in diagnostic radiology.

Eleven pregnant women had one or more abdominal X-ray examinations during the first three months of pregnancy. Subsequently, 8 had therapeutic abortion, whereas 3 went to term. The case histories are reported. The calculated foetal doses range from 0.03 to 3.7 r (0.01—18.9).

The author makes the following preliminary suggestions about irradiation during the first four months of pregnancy: Foetal doses below about one r do not indicate induction of abortion. Foetal doses between about one r and about ten r indicate therapeutic abortion only in the presence of additional indications. Foetal doses above about 10 r presumably always indicate abortion.

One of the pregnancies that was carried to term ought to have been interrupted. Four of the induced abortions ought not to have been performed.

X-ray examinations of the abdomen should not be performed during the first four months of pregnancy.

In order to avoid irradiation in the early stages of pregnancy, the following routine precaution is suggested: In fertile women X-ray examination of the abdomen should be carried out only during the first ten days after a regular menstrual period of normal intensity and duration.

I am greatly indebted to Professor Tage Kemp, the Institute of Human Genetics and Eugenics of the University of Copenhagen, to chief physician H. Hoffmeyer, Mødrehjælpsinstitutionen i København (the Danish Mothers' Aid Centre, Copenhagen), and to the heads of various anonymous mentioned departments, for kind permission to publish abstracts from their case histories.

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THE OESTROGEN LEVEL IN WOMEN AS DETERMINED BY CYTOHORMONAL INVESTIGATIONS OF VAGINAL SMEARS

COMPARISON WITH URINARY EXCRETION OF OESTROGENS AND ENDOMETRIAL BIOPSIES

By POUL FLINDT-HANSEN

As previously described by numerous authors (Papanicolaou, Pundel, de Allende & Orias, and others) the effect of oestrogen is reflected in the vaginal smear by the presence of superficial, acidophile cells while, conversely, predominance of intermediate and particularly basal cells indicates deficiency of oestrogen.

In order to determine hyper- and hypooestrogenism, limits of normal oestrogenism must first be established. This was undertaken by investigation of 24 normal menstruating women during 28 menstrual cycles. The vaginal smear was obtained, as a rule, by the women themselves with a dressed probe introduced into the vagina through a plastic tube of suitable dimensions and thereafter smeared on a slide. The preparations were stored in a dry condition until they were stained by a modified "Shorr method" as described in more detail by the author in a previous work (1957).

The *Acidophile Index (AI), i. e.*, the percentage content of superficial acidophile (red) cells, was determined daily and the values were indicated graphically so that an AI-graph was obtained of a type as shown by the example in Figure 1.

Each of the 28 AI curves may be divided into four phases: menstrual, postmenstrual, ovulative and premenstrual. The postmenstrual and premenstrual phases correspond to the low horizontal levels of the curve which are separated on the one hand from menstruation (characterized by blood stained preparations) and on the other, as a rule, distinctly delimited from the intermediate ovulative phase with the abrupt onset with a curve ascending to high levels and subsequently descending.

As regards the three intermenstrual phases in the 28 normal cycles investigated, outer limits (scatter) were calculated statistically both as

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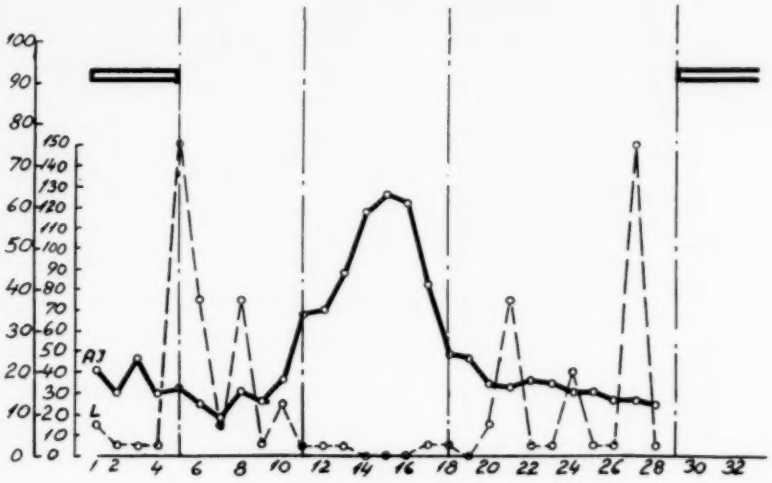

Figure 1.

The continuous AI curve indicates the content of acidophile cells day by day throughout a menstrual cycle. The interrupted curve shows the daily variations in the content of leucocytes, indicated by the ordinate up to 150. AI ordinate extends, as usual, to 100 per cent and the four phases of the cycle: menstrual, postmenstrual, ovulative and premenstrual are delimited by vertical lines. Mentruation is indicated by the enclosed rectangles.

regards the duration of the phase and for all the AI values in each individual phase as is shown in Table 1, where only the maximum value is given as regards the duration. The same conditions are shown graphically in Figure 2.

Table 1.

Outer limits for the acidophile index (AI) and the maximum duration of the intermenstrual phases. The two low phases were combined and, therefore, the duration of the longest is indicated.

	The two „low" phases: post-and premenstrual.	The „high" phase: ovulative
Outer limits for acidophile index (AI)	48 0	75 22
Maximum duration of phases in days	15 (Postmenstrual phase, however, only 11 days)	11

The normal AI curve (Figure 1) indicates the periodic undulation of the oestrogenic condition in relation to a cycle. Divergences from this exceeding the outer limits must arouse suspicion of oestrogen production deviating from normal so that, as is observed in Figure 2, AI values under 22 which persist for more than 15 days suggest hypooestrogenism and, conversely, AI values of over 48 maintained for more than 11 days indicate hyperoestrogenism. AI values between 22 and 48 are in the transition zone and for some cases may indicate hyperoestrogenism and for others hypooestrogenism when the condition persists for longer than 11 and 15 days respectively,

Thus, the duration and the absolute value of the acidophile index are equally significant in the question of normo-, hyper- or hypooestrogenism.

Table 2 shows the cytohormonal type distri-

Table 2.

The percentage content of acidophile and basal cells within the cytohormonal groups and the corresponding state of oestrogenism.

Cytohormonal type	Content basal cells. %	Content acidophile cells (AI) %	Oestrogenism
Dystrophic	None	Over 11 days: ≥48	Hyperoestrogenism
		Over 11 days: 48—22	Hyper- or hypooestrogenism
Hypotrophic high	None or few	Over 15 days: 48—22	
average		Over 15 days: 22—10	
low		Over 15 days: 10—0	
Atrophic slight	1—40		Hypooestrogenism
average	10—40		
marked	40—100		

bution which is employed in cases which deviate from the normal. The distribution is based upon the content of basal and acidophile cells in the vaginal smear which appears from the two centre columns, while the corresponding "oestrogenism" deduced from the conclusions previously mentioned is given in the last column of the Table. The atrophic and hypotrophic cytohormonal groups are expressions of hypooestrogenism and the dystrophic group, by and large, for hyperoestrogenism.

Figure 2 shows a diagram derived from Tables 1 and 2 for charting the AI values which, according to the above, must be followed for at least 15 days (in practice approximately three weeks) in order to express the state of oestrogenism.

Comparative investigations between the vaginal smear and the excretion of oestrogen in the urine which, according to the determinations by Pedersen-Bjergaard, are normally between 20 and 200 mouse units daily, showed agreement according to a series of authors (Rubenstein, Aepli et al., Magendie et al.); a high excretion of oestrogen corresponded to a dystrophic vaginal smear with high AI values (hyperoestrogenism) while, conversely, low "oestrogen figures" corresponded to hypotrophic with low AI values or even atrophic vaginal smear with atrophic cells (hypooestrogenism). (see also Table 2).

Good agreement was also obtained between the vaginal smear and biopsy of the endometrium in between 72 per cent and 92 per cent of the total number of determinations of each of the following authors: Ferin, Bernard et al., Albaux-Fernet et al., Pundel, Seibert, Stoll et al., Magendie et al.).

Dystrophic vaginal smear corresponds to endometrium in the proliferative phase while, on the other hand, it is more difficult to compare the vaginal smear with the endometrium in the secretory phase as the former, according to the majority of authors, only reflects the effect of progesterone to an uncertain extent while this is definitely observed in the endometrium.

RELATIONSHIP BETWEEN CYTOHORMONAL INVESTIGATION AND EXCRETION OF OESTROGEN IN THE URINE

The material comprises 34 patients suffering from amenorrhoea. From five to seven oestrogen analyses were undertaken per patient making a total of 164. These analyses were undertaken partly prior to stimulation treatment with gonadotrophic hormone and partly in connection with such treatment.

Table 3.

Results of 164 oestrogen analyses in 34 patients distributed between the two groups: "prior to" and "during and after" treatment with gonadotrophic hormones.

	No. Cases	Agreement between oestrogen analyses and acidophile index
Group I (prior to treatment)	34 (70 oestrogen analyses)	31 (91%)
Group II (during and after treatment)	26 (94 oestrogen analyses)	22 (91.5%)
Total	60	

Table 3 shows agreement between the cytohormonal investigation and the excretion of oestrogen in the urine (determined as described above) in more than 90 per cent of the cases investigated.

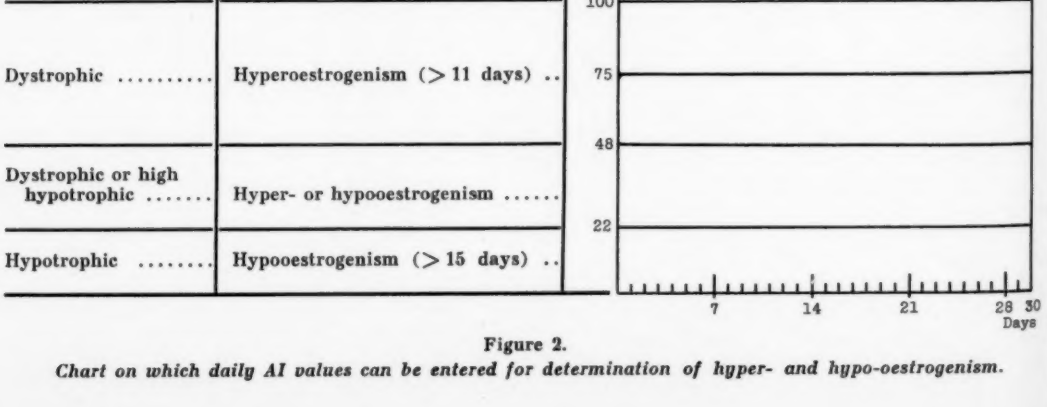

Figure 2.

Chart on which daily AI values can be entered for determination of hyper- and hypo-oestrogenism.

RELATIONSHIP BETWEEN CYTOHORMONAL INVESTIGATION AND ENDOMETRIAL BIOPSIES

This material comprises 55 endometrial biopsies, *viz*, 34 in the proliferative phase, 13 in the secretory phase and eight which showed atrophy.

In the first group approximately 91 per cent (31 cases) were in agreement with the cytohormonal investigation which revealed dystrophic AI curves with predominantly high AI values.

In the second group which comprises biopsies in the secretory phase, it was, as mentioned previously, difficult to compare with the vaginal smear in which the effect of progesterone is manifest to a very uncertain extent. Only half of the cases showed the so-called "progesterone picture" in the vaginal smear and on comparison with a corresponding number of endometrial biopsies in the proliferative phase the author found, after a preliminary fall in the AI curves, "progesterone picture" in the vaginal smear also in half of the cases. This disagreement between the findings in the vaginal smear and the endometrium confirms the uncertainly in the evaluation of the effect of progesterone upon the vaginal epithelium.

In the third group in which the endometrium was in the atrophic phase, only one of the eight cases investigated showed an atrophic vaginal smear (80 per cent basal "atrophic" cells). Thus, only this one case showed agreement with the endometrium while the remainder showed evidence of quite considerable oestrogen effect in the vaginal smear (five of the cases had AI of 40—50) in contrast to the atrophic endometrium. The vaginal epithelium must thus possess greater sensitivity to oestrogen than the endometrium. This will be discussed in greater detail in subsequent paragraphs.

In the proliferative group the cytohormonal investigation agreed with the endometrial biopsy in 91 per cent while in the atrophic group, with the exception of one case, there were deviations between the findings in the two methods of investigation. The proliferative group and the atrophic group are expressions of two different oestrogenic levels. The low level in the latter group is not sufficient to produce the proliferative phase in the endometrium but, however, sufficient to produce a not inconsiderable acidophilia in the vaginal smear. Not only is the endometrium slower to react but it has a higher threshold for the influence of oestrogen than the vaginal epithelium and for this reason the hormonal reaction in the two "receptors" is not always identical. This phenomenon is very pronounced in the atrophic group. The observation that in the proliferation group such good agreement was obtained between the two methods of investigation must be due to the higher oestrogen levels which not only produced a massive acidophilia in the vaginal smear but also produced the proliferative phase in the endometrium.

SUMMARY

The acidophile index, AI (percentage content of red acidophile cells in the vaginal smear) was determined for 28 normal menstrual cycles and the corresponding AI curves divided into three intermenstrual phases clearly delimited from one another, *viz*, postmenstrual, ovulative and premenstrual. Concerning each of these three phases the outer limits (scatter) for the *acidophile index* and for the *duration of the phase* were calculated and from these normooestrogenism is defined as a periodic variation between various AI levels, which individually should not last for more than a couple of weeks. If the same values are present for longer periods than those stated, conditions of hyper- or hypooestrogenism are concerned. The limits for these are recorded both as regards the AI level and the duration of the phase.

Out of 60 cases in which the excretion of oestrogen in the urine was analysed, agreement with the cytohormonal investigation was found in 90 per cent. Endometrial biopsy during the proliferative phase showed agreement in over 90 per cent while endometrial biopsy in the secretory phase could not be compared directly with the vaginal smear where the effect of progesterone does not become sufficiently distinctly manifest. Endometrial biopsies of atrophic type were in agreement only to a very limited extent with the vaginal smear on account of the differing hormonal sensitivity of the vaginal epithelium and the endometrium.

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THE VAGINAL SMEAR IN AMENORRHOEA AND ITS REACTION TO THERAPY

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The vaginal smear in amenorrhoea has been studied by Papanicolaou and his co-workers, Bertelsen, Pundel, de Allende & Orias and other authors.

The present material comprises 49 patients with amenorrhoea between the ages of 15 and 40 years. In six of the cases, the amenorrhoea was primary while in the remaining 43 cases it was secondary.

Table 1 shows the distribution of cases. This distribution is similar to that of other authors (de Allende & Orias, Pundel).

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Thus, in approximately three quarters of the cases of amenorrhoea, deficiency of oestrogen is observed (hypotrophic and atrophic groups) while pathologically increased oestrogen production was present in the remaining cases (dystrophic group).

Cytohormonal investigation during treatment.

The treatment was undertaken with the gonadotrophin preparations Antex® (gonadotrophin from mares' serum) and Physex® (chorion gonadotrophin), manufactured by "Løven's kemiske Fabrik", Copenhagen, and administered according to the dosage proposed by Rydberg et al. (7, 8, 9). A crystalline solution of 10 mg oestradiol monobenzoate (Follicyclin®, Ciba) was employed for the oestrogenic therapy.

Table 1.
Distribution of the cases of amenorrhoea with regard to the cytohormonal types.)*

Oestrogenism	Cytohormonal type		Number	Percentage	
Hypooestrogenism	Atrophic	marked .	3	6.1	20.4
		average .	2	4.1	
		slight ...	5	10.2	
	Hypotrophic	low	17	34.7	53.1
		average .	9	18.4	
		high ...	0		
	Dystrophic		12	24.5	
Hyperoestrogenism	Uncharacteristic		1	2.0	
	Total		49	100.0	

*) See previous article regarding subdivision according to the cytohormonal types.

Table 2.
Results of treatment and the corresponding phases of the endometrium.

Therapy (injection)	No subsequent bleeding	With subsequent bleeding				Total
		Phase of endometrium			No Biopsy	
		Prolif.	Secr.	Atrophy.		
Antex + Physex	14	5	3	1	4	27
Antex	3				2	5
Physex	2	2	3			7
Follicyclin	1	2				3
Follicyclin + Physex ..		1				1
Total	20	10	6	1	6	43
No Therapy	5	2	1		1	9

It appears from Table 2 that, by and large, only half of all the cases treated and of the cases treated with Antex-Physex alone reacted with bleeding. Out of 14 endometrial biopsies in the Antex-Physex group and the Physex group together, only six showed a secretory phase and thus the full effect of therapy. The remainder of the cases were in proliferative or atrophic phases.

These results do not correspond entirely to those previously obtained with treatment with Antex-Physex (Riisfeldt, Rydberg et al., Østergaard) but this may be explained by the fact that the present material comprises cases which had resisted several previous attempts at treatment. In a more average material, more favourable results would undoubtedly have been obtained.

It will be observed from Table 3 that a definite increase in the AI in relation to combined therapy with Antex-Physex, according to this material, will be followed by bleeding while, conversely, no haemorrhage occurs, as a rule, when AI-increase does not occur.

Figures 1 and 3 show two cases with AI-increase and bleeding following combined Antex-Physex therapy while Figure 2 shows no AI-increase and corresponding absence of bleeding.

Table 3.
Increase in the acidophile index following combined Antex-Physex therapy in the two groups, with and without bleeding.

Acidophile index (AI)	Bleeding	No bleeding	Total
Increase	10	4	14
Indefinite or slight increase	2	1	3
No increase	1	9	10
Total	13	14	27

Table 4.
Increase in the excretion of oestrogen following combined Antex-Physex therapy in the two groups: with and without bleeding.

Excretion of oestrogen	Bleeding	Without bleeding	Total
Definite increase ..	6	1	7
Doubtful increase..	2	2	4
No increase	1	9	10
Total	9	12	21

Table 4 shows that, as with the AI, the excretion of oestrogen increases in the majority of cases in which Antex-Physex stimulation results in haemorrhage (Fig. 3) while the excretion of oestrogen (and the AI) do not increase when no haemorrhage follows the therapy (Figure 2).

Haemorrhage from the endometrium (and preferably in the secretory phase), increase of the acidophile index (AI) and excretion of oestrogen are all signs of the effect of therapy.

The two last methods of investigation show good mutual agreement as the acidophile index and the excretion of oestrogen either both reacted or remained uninfluenced by the treatment. Three cases only (15 per cent) out of a total of

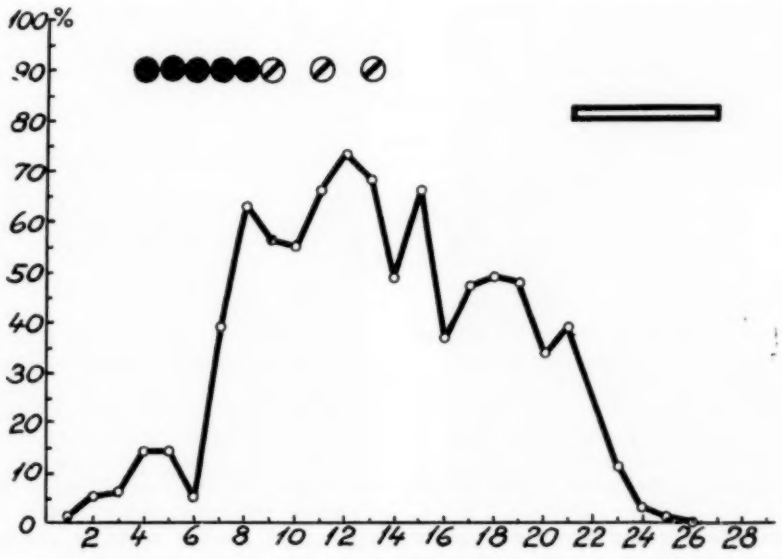

Figure 1.
Marked increase in acidophile index (AI) following Antex (1,500 I.U. × 5) (black circles) + Physex (1,500 I.U. × 3) (crossed circles). Therapy was followed by bleeding (enclosed rectangle).

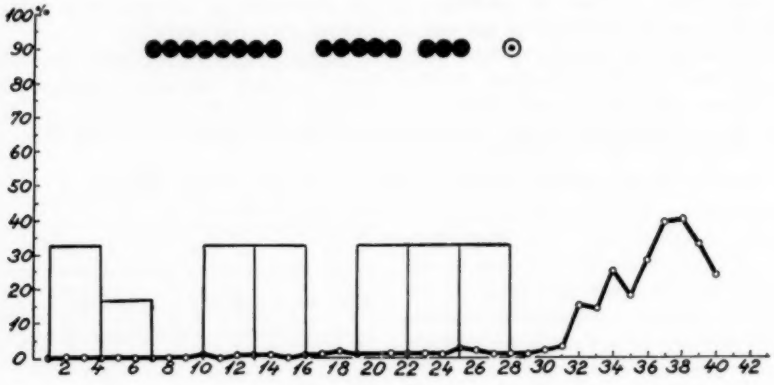

Figure 2.

Low hypotrophic AI curve in a female aged 25 years with primary amenorrhoea.

No AI-increase following Antex (3,000 I.U. × 8, then 5,000 × 5 and, finally 9,000 I.U. × 3) (black circles) but immediately after injection of 10 mg Follicyclin (circle with black centre).

The columns indicate the excretion of oestrogen which did not alter during the treatment but remained constant at 33 M.U. per 24 hours. Excretion of gonadotrophin: 10—15 R.U.

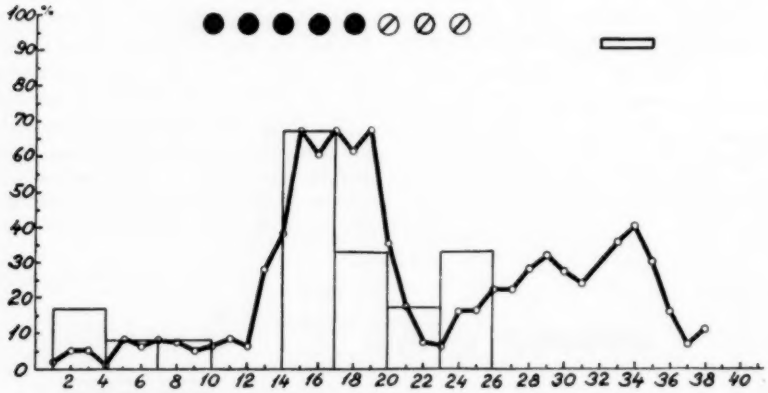

Figure 3.

Low hypotrophic AI curve (prior to treatment) from a woman aged 24 years with secondary amenorrhoea.

Increase of both AI and excretion of oestrogen (columns) (17, 8, 8, 67, 33, 17, 33 M.U. per 24 hours) and bleeding following Antex (2,000 I.U. × 5) (black circles) + Physex (1,500 I.U. × 3) (crossed circles). Excretion of gonadotrophin: 10, 7 and less than 5 R.U.

21 cases showed disagreement as reaction was demonstrated by only one of the methods.

Out of five cases in which Antex treatment was employed alone (Table 2) one of the cases in which bleeding occurred showed increase of AI and of the excretion of oestrogen. The same reaction was observed for AI in one case without haemorrhage as appears from Figures 4, 5 and 6. Thus, in the last case, therapy caused increase in the AI but was not sufficient to produce bleeding from the endometrium.

The latent period for the increase in AI, calculated from the first injection of Antex until the commencement of the increase was, in the majority of cases, between two and eight days (average less than five days). A few cases showed a latent period of between 10 and 17 days but it is difficult to elucidate whether this was an expression of a late reaction or a spontaneous increase of the AI quite independant of the treatment.

Physex treatment alone (Table 2) rendered quite good effects. Bleeding occurred in five cases, three of which were in the secretory phase.

In all of the cases, the vaginal smear showed considerable oestrogen effect prior to therapy (dystrophic or high hypotrophic AI curves) and

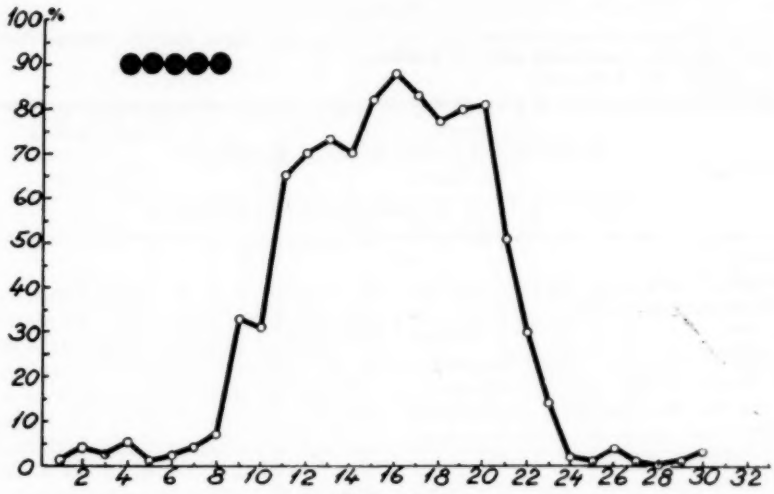

Figure 4.

Low hypotrophic AI curve (prior to treatment) in a woman aged 24 years with secondary amenorrhoea. Following administration of Antex (1,500 I.U. daily for five consecutive days) (black circles) a marked increase in the AI was observed. Same case as in Figures 5 and 6.

a fall in the AI level after the treatment in five cases out of seven. This is not, however, a specific sign of the effect of progesterone (as a sequel of possible rupture of a follicle and corpus luteum formation) but might also be a spontaneous fall in the AI.

Table 2 shows that after treatment with oestrogenic hormone three cases reacted with haemorrhage. In all four patients an increase in the AI occurred after oestrogenic therapy (Figure 2). The observation that the endometrium was only in the proliferative phase was to be anticipated.

In nine patients (Table 2) no treatment was administered. In four, spontaneous haemorrhage occurred. In the five cases in which no haemorrhage occurred the cytological picture, as might be anticipated, was more atrophic compared with the cases in which haemorrhage occurred.

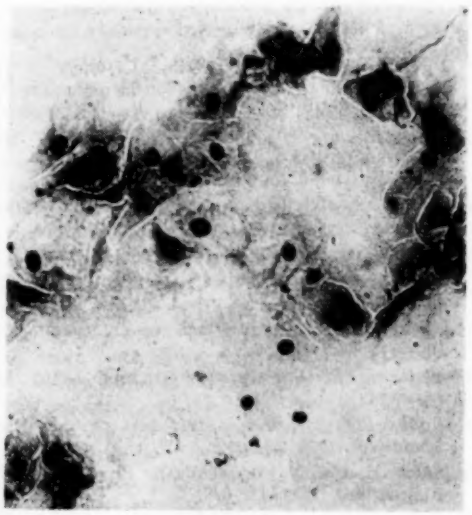

Figure 5.

Secondary amenorrhoea for 2—3 years. Low hypotrophic cytohormonal picture with small and medium intermediate cells with pyknotic nuclei. No genuine basal cells and less than 5 % acidophile cells. Same case as in Figures 4 and 6.

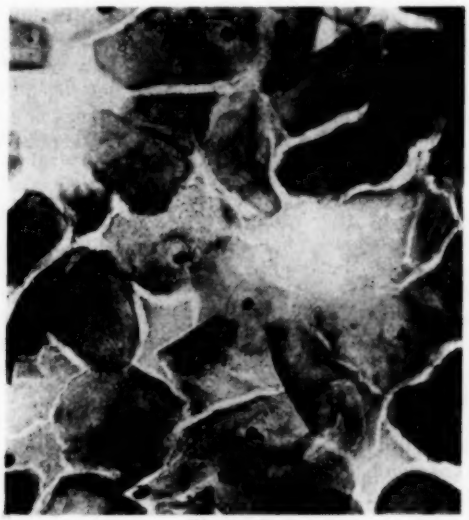

Figure 6.

Following Antex therapy a very considerable increase was observed in the number of acidophile cells to approximately 80 per cent and a corresponding "clearing" of the picture. Same case as in Figure 4 and 5.

Table 5.

Subdivision of all 49 cases of amenorrhoea into the cytohormonal types and the various treatment-groups within the two categories: with and without bleeding.
A: Antex. P: Physex. F: Follicyclin.

Cytohormonal type	Bleeding					Without bleeding					Total
	Treatment					Treatment					
	A+P	A	P	F	No. treat.	A+P	A	P	F	No. treat.	
Atrophic { Marked				1		2					3
Atrophic { average						1				1	2
Atrophic { slight	4									1	5
Hypotrophic { Low	5			1	2	5	1		1	2	17
Hypotrophic { average	2	1			1	2	1	1		1	9
Hypotrophic { high											
Dystrophic	1	1	4	1	1	3		1			12
Uncharacteristic						1					1
Total	12	2	4	3	4	14	2	2	1	5	49

VALUE OF THE CYTOHORMONAL INVESTIGATION FOR DETERMINATION OF PROGNOSIS AND CHOICE OF THERAPY

It appears from Table 5 that the prospects of menstruation after treatment with gonadotrophic hormones are slight in cases with genuine atrophic vaginal smear with deep cells in considerable numbers (marked and average atrophic groups) while in the slightly atrophic group and in the hypotrophic group bleeding occurred in 12 cases out of 22 (with combined Antex-Physex therapy in 11 out of 18 cases).

Out of the four cases to which oestrogen therapy was administered, bleeding ensued in three including one markedly atrophic case.

In hypotrophic and atrophic cases with reduced ovarian function, combined Antex-Physex therapy is indicated while in dystrophic cases where a continual predominantly increased oestrogen formation from one or more ovarian follicles is concerned, treatment with Physex alone should be instituted to produce luteinization.

In resistant cases in which no effect is expressed in the vaginal smear and where no bleeding occurs, substitution therapy may be considered: in hypotrophic and atrophic cases oestrogen therapy and in dystrophic cases progesterone therapy. Treatment with steroid sex hormones or substances with similar actions must not be expected to exert any prolonged effect upon the ovarian function.

Treatment of amenorrhoea should, therefore, primarily be undertaken with gonadotrophic hormones and only if this fails are steroid sex hormones or substances with similar actions indicated.

SUMMARY

The cases of amenorrhoea mentioned are subdivided into atrophic, hypotrophic and dystrophic cases. Treatment should consist mainly of stimulation therapy with gonadotrophic hormones. In approximately half of the cases bleeding ensued and, simultaneously, increase of the AI values occurred while, conversely, cases without bleeding, by and large, did not show any increase of the AI curve.

The latent period for increase in the AI averaged five days.

Finally, the prognosis and the indications for treatment of amenorrhoea are mentioned as judged from the cytohormonal types.

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ABDOMINAL AORTOGRAPHY IN DISEASES OF THE ARTERIAL SYSTEM

By PER DAMGAARD-MØRCH, OLAF PETERSEN and ERIK SANDØE

Abdominal aortography as a procedure in clinical diagnosis has been employed since 1949 in Medical Department B and the Radiological Department of the University Hospital. As of recent date, a total of one hundred examinations had been carried out in these two departments on patients referred for observation for diseases of the arteries in the abdomen or pelvis. A total of ninety-one patients were examined, eighty-two of them once and nine of them twice.

TECHNIQUE

In sixty-seven cases, the contrast medium was injected through a polyethylene catheter introduced percutaneously into the femoral artery by means of a modified Seldinger technique(Thomsen & Tybjærg Hansen, 1954). The femoral artery pulse in these patients was perceptible on at least one side, and in no case did the arterial puncture involve any difficulty. In sixty-four of the cases the catheter could be advanced into the aorta after introduction and placed in the ideal position with the tip on the level of the intervertebral disk between the IV and V lumbar vertebrae, while in three of the cases it proved impossible to advance it further than the aortic bifurcation. In these last three cases, as well as in thirty-three of the patients in whom the catheter could be advanced into the aorta without difficulty, aortography showed stenosing arteriosclerotic lesions of the common iliac artery or the external iliac artery on the side where the catheter had been introduced.

In the remaining examinations, the contrast medium in twenty cases was in injected by needle after direct translumbar puncture of the aorta, and in thirteen cases through a polyethylene catheter introduced percutaneously into the brachial artery and advanced from here to the thoracic and abdominal aorta (Radner 1958, Thomsen & Tybjærg Hansen 1954).

The contrast injection by the translumbar method was done with a 50 ml all-glass syringe with a wide bore, while for the transfemoral and transbrachial procedure, a metal syringe with a lever arrangement (Jönsson 1949) was used at first, and an automatic high-pressure syringe in the last twenty examinations (Gidlund 1956).

Urografin® 60 per cent is now always used as radiopaque dye, while previously Diodone® 50 percent, Diaginol® 30—50 per cent or Diodrast® 70 per cent, were used. In those examinations where the transfemoral or translumbar route was employed, a good contrast filling was obtained using 20—25 ml radiopaque dye, while quantities amounting to 40—60 ml were usually required in the transbrachial approach.

Casette changing was carried out manually in the first three examinations, while an automatic film changer was used in the subsequent examinations. The exposure rate has varied somewhat in the course of time. The current procedure is to take one picture per second for ten seconds.

COMPLICATIONS

Serious complications occurred in three cases among the one hundred examinations. In two of these, the patients developed oliguria and rising blood urea following the examination. Diuresis was re-established in one case, and on examination fourteen days later the renal function was found to be normal. In the other case, death ensued in the course of some ten days. Autopsy showed a stenosis of the abdominal aorta just below the origin of the renal arteries, fresh thrombus formations at these points and severe endarteritic lesions in the kidneys. The examination had been by the transbrachial route, 60 ml of 70 per cent Diodrast being injected.

In the third patient, severe pain developed in the one leg a little over three hours after the examination, the leg becoming pale and the femoral pulse impalpable. The ischaemic symptoms decreased only slightly during the followning days, so, as a last resort, thrombectomy was attempted two weeks later. The attempt failed, the patient's condition deteriorated after the operation, and death occurred in uremia after another 14 days. The abdominal aortography had revealed severe arteriosclerotic lesions of the abdominal aorta and of both common iliac arteries, the lumen in the later arteries being reduced in diameter to 2—3 mm. At a later stage of the explorative operation, arteriography had been carried out with contrast injection in both commen iliac arteries. Hereby, complete occlusion of the common iliac

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artery was found on the side giving the symptoms, while it was still possible to demonstrate a narrow lumen in the vessel on the opposite side. The abdominal aortography had been done transfemorally, the catheter being introduced via the femoral artery in the leg which developed the severe ischaemic symptoms following the examination. Twenty-five ml 60 per cent urografin was injected.

There can hardly be any doubt that the injection of radiopaque dye was the cause of the renal damage in the first two patients, as the renal function had been determined in both prior to the examination and found normal in the one and moderately reduced in the other. In the third patient, on the other hand, the cause of the conversion of the incomplete thrombosis in the common iliac artery into a complete thrombosis is difficult to decide. Most probably a spontaneous progression of the disease has taken place, but an acceleration of the process may have resulted from the injection of the contrast medium. No signs of catheter lesions in the arterial wall were revealed at autopsy.

In one case the roentgenograms showed that all the radiopaque material had been injected sub-intimally. This occurred in a patient with severe arteriosclerosis of the common iliac arteries and the aorta. The catheter had been introduced via the femoral artery and from here advanced into the aorta, where its tip had presumably damaged the intima. The patient experienced no inconvenience of any kind from the accident, and the examination was repeated a few days later with satisfactory results, the radiopaque medium being injected into the aorta this time through a catheter introduced transbrachially. Apart from that, no complications were observed which could be associated with the introduction of the polyethylene catheter or with the puncture of the aorta.

RESULTS

In seventy-three cases, a good visualization was obtained of all major abdominal and pelvic arteries on the first attempt. In fifteen cases the iliac arteries were only partly visualised. In eleven instances the field had been centred too low, and in four cases only the most inferior portion of the aorta had been opacified. In three cases the contrast filling was poor because it had been impossible to advance the transfemoral catheter above the aortic bifurcation, and in the last case, where the examination had been performed by the translumbar route, the aorta had been pierced too far caudally. The examination failed in three patients, too little contrast medium being used in two cases and the injection of radiopaque dye being subintimal in the third case, as mentioned previously.

In seven cases where aortography had provided insufficient information on the first attempt, the

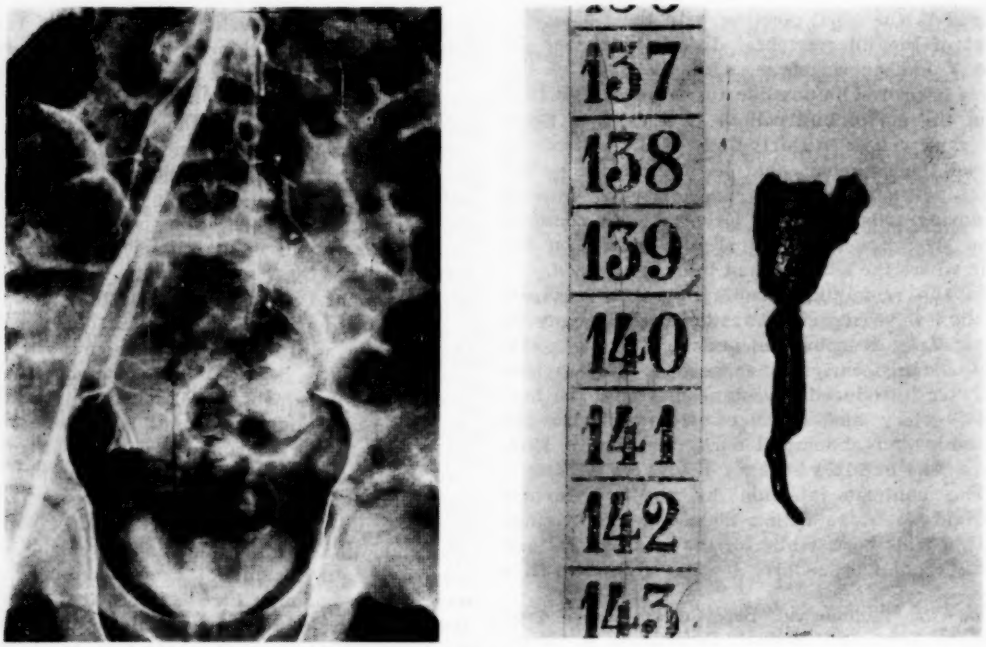
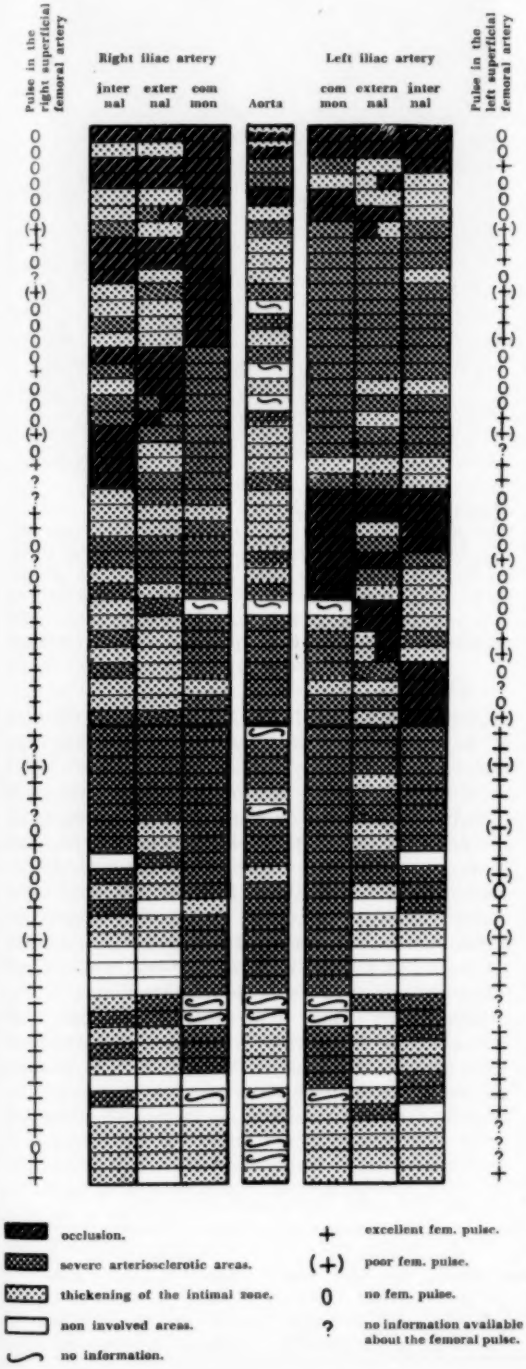


Fig. 1.
Saddle embolus in a fourteen-year-old girl with rheumatitic heart disease. Aortography shows filling defect in the inferior part of the aorta. No filling of the left iliac arteries. The other picture shows the removed embolus.

Table 1.

Aortographic findings in 67 patients with arteriosclerotic disease.

The vertical columns represent the different arterial segments and each horisontal line denotes the findings in the single patient.



examination was repeated with a completely satisfactory result. In four cases the transbrachial technique was used on the second trial, *viz.*, in three patients in whom it had been impossible to advance the catheter far enough into the aorta, and in one patient in whom the radiopaque dye had been deposited sub-intimally. One case was examined thrice.

Seventy-eight patients were referred for examination with symptoms of reduced blood supply to one or both legs. In nine of them, the aortographic findings showed normal conditions in the abdominal and pelvic arteries, in one of them a short narrow stenosis was demonstrated in the abdominal aorta, immediately below the origin of the renal arteries, and in another an embolus in the left iliac artery was demonstrated. The last case was that of a 14-year-old girl with rheumatic heart disease. The day before the examination she had suddenly developed symptoms of reduced blood supply to the left leg, and on arteriography (Fig. 1 a) an incomplete contrast filling was found in the most inferior part of the abdominal artery and in the common and external iliac arteries on the side giving symptoms, while nothing abnormal could be demonstrated in the remaining vessels. The patient was operated on, and in agreement with the roentgenographic picture a four-cm-long embolus was found, straddling the aortic bifurcation, and projecting from here into the common iliac and external iliac arteries on the left side.

Lesions of arteriosclerotic origin were demonstrated in the remaining sixty-seven of the seventy-eight patients with ischaemic symptoms arising from the legs (Table 1). In four of the cases, the lesions merely consisted of rounded filling defects along the vessel walls, presumably due to thickenings of the intima (L i n d b o m 1950). In sixty-three cases, stenosis or occlusion of the lumen was also found in one or more arteries, indicating that the arteriosclerosis was complicated by thrombus formation. In cases with complete occlusion of an arterial segment, delayed but satisfactory retrograde contrast filling of the vessel peripheral to the occlusion was usually observed, through large inter-arterial anastomoses, which arose both from more centrally placed vascular sections on the same side and from the arteries on the opposite side of the pelvis and abdomen.

There were wide-spread processes in the majority of the patients, and in only two patients were severe lesions demonstrated, localized to a single short vascular section. Complete occlusion of the common iliac artery and the external and internal iliac arteries was frequently found, but only rarely occlusion of the aorta (Table 2). If stenosis and occlusion are grouped under one heading, it is seen that the common iliac artery was that vascular section most frequently affected (Table 2), and that the lesions here were bilateral

Table 2.

Incidence of stenosing and occluding arteriosclerotic lesions in the various arterial sections. The table covers 54 patients in whom severe lesions were demonstrated, while 9 have been omitted in whom the aortography visualized only the condition in the iliac artery.

	Occlusions	Stenoses	No or only slight lesions
Abdominal aorta	3	30	21
Right common iliac artery ..	12	37	5
Left common iliac artery ..	11	38	5
Right external iliac artery ..	9	13	32
Left external iliac artery ..	11	20	23
Right internal iliac artery ..	10	18	26
Left internal iliac artery ..	11	23	20

in about 90 per cent of the patients, while for the external and internal iliac arteries this was the case in only about 60 per cent of the patients (Table 3). With one exception, all the rather severe lesions in the abdominal aorta were located in the distal one-third of the vessel below the origin of the renal arteries, and as a rule the lesions were associated with more severe or equally severe processes in the common iliac arteries. Arteriography of the lower extremities was subsequently performed in 32 of the patients, and occlusions were demonstrated in the femoral or popliteal arteries in 22 of them.

The majority of the patients with severe arteriosclerotic lesions were men between the ages of 55 and 65 years, and none of them was under 40 years of age. They all complained of intermittens claudication; 25 of them had pain while at rest, 27 had slight trophic changes and five had commencing gangrene of one or more toes. In a 50-year-old woman, the symptoms had had a sudden and violent onset one month prior to the examination, while in the other patients they had developed more slowly; over a period of six months in six patients, one year in five patients, five years in twenty-eight patients and five to twenty years in 23 patients. No relationship could be observed between the duration of symptoms and the extent or degree of severity of the lesions. In the case where the ischaemic symptoms had shown an acute and violent onset one month prior to the examination, there was complete occlusion of the abdominal aorta from the origin of the inferior mesenteric artery, of both common iliac arteries, and of the internal and external iliac arteries on the left side (Fig. 2). The patient died shortly afterwards, following a surgical attempt at thrombectomy. Autopsy fully confirmed the operation findings.

Fig. 2.

Severe arteriosclerotic lesions in a 50-year-old woman, who developed severe ischaemic symptoms from the left leg one month before examination. No contrast medium is seen in the aorta below the origin of the inferior mesenteric artery. Retrograde filling of the external and internal iliac arteries on the right side occurs through a well developed network of collateral arteries.

The femoral pulse was found to be absent or definitely weakened on both sides in all cases of occlusion of the aorta as well as in bilateral occlusion of the iliac arteries. In unilateral occlusions of the common iliac or external iliac artery, the femoral artery pulse was absent or reduced on the corresponding side in eighteen patients and normal in three patients. Two of the latter patients had an occluding thrombus in the external iliac artery, and the third patients had an occlusion of both the external and common iliac arteries. In patients with stenosing processes in the aorta and iliac arteries, a normal femoral pulse was found in about three-quarters of

Table 3.

Incidence of bilateral and unilateral lesions in 63 patients with severe arteriosclerosis.

	Bilateral lesions				Unilateral lesions		
	Occl.-occl.	Occl.-sten.	Sten.-sten.	Total	Occl.	Sten.	Total
Common iliac artery	3	16	32	51	2	4	6
External iliac artery	3	8	12	23	9	11	20
Internal iliac artery	2	8	19	29	10	9	19

the cases and a reduced or absent femoral pulse in about one-quarter of the cases.

Two patients with thrombosis were operated on; arteriography after the operation showed that the vascular grafts were functioning satisfactorily in both cases.

Three patients were referred for examination as a pulsating tumour had been felt in the abdomen. An aneurism of the abdominal aorta was found in the first, an aneurism-like dilatation of both common iliac arteries and both external iliac arteries was found in the second, and arteriovenous aneurisms of the true pelvis were found in the third.

Finally, eight children were examined for an isolated "gigantism" of the one leg. The arteries to the enlarged extremity showed a slight hyperplasia in four of them; normal conditions were found in the others.

In all except four patients, the blood urea was determined prior to the examination. It was normal in 84 patients and moderately increased up to a maximum of 60 mg per 100 ml in three patients.

DISCUSSION

In the present material, all patients with stenosing or occluding arteriosclerotic processes had been referred for arteriography to decide whether vascular surgery might increase the supply of blood to one or both legs. Examination of these patients, who had severe ischaemic symptoms from the lower extrenities and normal or only slightly raised blood urea, led to conclusions which may be summed up as follows:

1. In arteriosclerosis, wide-spread stenosing or occluding processes are often found simultaneously in several of the arteries of the abdominal and pelvic cavities. The isolated occurrence of severe lesions in a single limited vascular section is found only exceptionally. Similar observations have been reported previously by Gottlob (1952), Wanke (1953) and others.

2. Stenosing or occluding arteriosclerotic lesions in the abdominal aorta are almost always located in the distal one-third of the vessel below the origin of the renal arteries, and usually occur together with more severe or equally severe lesions in both common iliac arteries. As first suggested by Leriche (1946), an obvious explanation of this state of affairs is that the arteriosclerotic and thrombotic lesions primarily commence in the common iliac arteries and spread from here into the aorta. The common iliac arteries were the vascular section most frequently showing severe lesions, which lends further support to this theory.

3. If considerable arteriosclerotic lesions in the arteries of the abdomen and pelvis are found, stenosing or occluding thromboses of the femoral or popliteal arteries frequently occur. The present material gives no definite indication as to how frequently occluding processes can be demonstrated in the more central vessels when thromboses of the arteries of the lower limbs are present. According to Wanke (1953), this occurs in about 33 per cent of the cases.

4. The patient's history provides no opportunity for distinguishing with certainty between thrombosis and embolism, as even very severe and extensive thrombitic lesions in the arteries of the abdomen and pelvis can initiate with acute and violent ischaemic symptoms from the legs. Gottlob (1952) and Schrader (1955), as well as several others, have previously drawn attention to this.

5. A feeble or absent femoral pulse on both sides usually indicates occluding or stenosing processes in the aorta or bilaterally in the iliac arteries, while reduced pulsation in one of the femoral arteries suggests occlusions or stenoses in the iliac arteries on the corresponding side. In occlusions of the aorta, normal pulsation in the femoral artery will hardly be found, but on rare occasions it may be found in occlusion of the extrenal iliac and common iliac arteries, and fairly frequently in stenosing lesions in the aorta and iliac arteries on the corresponding side. It may be reported in this connection that Wyllie et al. (1953) found a palpable femoral pulse in 26 out of 27 patients with stenosing processes in the pelvic arteries, and that Schrader (1955) has reported a patient with an occluding thrombosis of the external iliac artery and normal pulsation in the femoral artery.

There is thus much in favour of the conception that in arteriosclerotic vascular lesions, the vascular section from the abdominal aorta down to and including the popliteal arteries constitutes a unit; abdominal aortography is therefore indicated prior to vascular surgery, both in suspected occlusions in the arteries of the abdomen and pelvis, and in cases where a surgically accessible thrombus in one of the arteries of the leg has been demonstrated primarily. In the former cases, in order to safeguard against lesions of such an extent as to preclude surgical intervention, and in the latter cases, to exclude the possibility of more severe lesions centrally, which can compromise the functional result of a peripheral anastomosis operation.

As numerous studies have shown (McAfee et al. (1956), Damgaard-Mørch et al. (1957) Idborhn (1956 and Schrader (1955)), and as the material presented here has confirmed, abdominal aortography not infrequently involves serious complications. The risk appears to be least in the transfemoral technique. As the translumbar and as opposed to the transbrachial technique, the transfemoral approach results in a rapid and effective mixing of the contrast medium with a large volume of blood, the radiopaque dye being injected directly opposite to the blood flow. The examination can thus be made with a rela-

tively small amount of radiopaque dye, with little danger of renal damage, while the transbrachial method, where the injection takes place in the direction of blood flow and where the mixing is slight, requires a greater amount of contrast medium, but nevertheless often gives poor and inadequate visualization of the arteries. In addition, the transfemoral technique, like the transbrachial but unlike the translumbar technique, does not involve any danger of haemorrhage and provides complete certainty that the entire amount of radiopaque dye will be injected into the aorta and not into one of its side branches, as the position of the catheter tip is checked by a trial exposure before the examination.

The method can be used in the majority of patients with arteriosclerotic lesions of the arteries, provided there is a palpable femoral pulse, but in complete occlusions, and in a few cases of stenosing processes of the aorta or bilaterally in the iliac arteries, there is no alternative to carrying out the examination translumbally or, if necessary, transbrachially. Of these two methods we prefer the translumbal one, as the transbrachial method, as mentioned, often gives an incomplete visualization of the vascular system, and at the same time requires greater amounts of radiopaque dye, thereby increasing the risk of renal damage, a risk already exceedingly great in patients suffering from occlusive processes of the inferior part of the aorta (McAfee et al. (1956)).

SUMMARY

The technique, complications and diagnostic results in one hundred abdominal aortographies are discussed. It is stressed that in patients over 40 years of age who have ischaemic symptoms from the lower extremities, very widespread stenosing or occluding arteriosclerotic processes in the arteries of the abdomen and pelvis can often be demonstrated, that an isolated occurrence of severe arteriosclerotic lesions in a minor vascular section in the same region is very rare, and that thromboses of the arteries of both the pelvis and legs are relatively frequent findings in the same patient. Further, examples are presented where patients with considerable stenosing or occluding processes in the iliac arteries can have normal pulsation in the femoral arteries, and it is concluded that abdominal aortography is indicated prior to vascular surgery, both in cases where occlusions in the vessels of the abdomen or pelvis are suspected, and in cases where surgically accessible arteriosclerotic lesions of the arteries of the legs have been primarily demonstrated. The authors prefer the transfemoral technique, at it involves least risk, and state that it can be used in the majority of patients with arteriosclerotic vascular lesions, provided merely that the femoral pulse can be felt on one of the sides.

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